

Sulfonamide Therapy in Medical Practice

by

FREDERICK C. SMITH, M.D., M.Sc. (Med.), F.A.P.S.

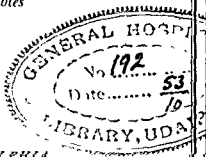
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Foreword by

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*Illustrated with
Numerous Engravings, Graphs
and Tables*



PHILADELPHIA

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To

My Wife

*upon whom I can depend
for helpful and needed encouragement
and for constructive criticism
when it is due
this volume is affectionately dedicated.*

Preface

THE dream of a chemical agent which will destroy pathogenic microorganisms within the body and which at the same time is harmless to the body organism has been a guiding force of a host of medical scientists for many decades. Ehrlich had it and was indefatigable in his laboratory in the search for such a medicament, finally bringing forth salvarsan, which with its modification, neosalvarsan, is still a standard treatment for syphilis.

No other significant chemotherapeutic addition to the armamentarium against disease made its appearance until prontosil and then sulfanilamide burst forth with dazzling brilliance. The chemicals were not new; they had been known since 1908, but heretofore no one had discovered that they had a vital therapeutic rôle. Once this discovery was made, however, the sulfonamides began to dominate medical literature as, one after another, new members of the family were developed. So intense, indeed, has been the interest of the profession in this new and potent group of drugs that it has been unusual in the past five years to pick up a medical journal without finding an article about or some reference to them.

Unfortunately, however, destructive as the sulfa drugs are to certain pathologic organisms, they do not fulfill the second requirement of an ideal chemotherapeutic agent, that of being harmless to the human host. All of the sulfa drugs have toxic properties in varying degrees and their use calls for the *art* of medicine to at least as high a degree as with any other therapeutic agent. Also, it must be constantly remembered that they are not cure-alls. It is with the intention of pointing out the possibilities of the sulfonamides and to emphasize their limitations and their toxic properties that this book has been written.

Sincere thanks are hereby given to the many authors and to the medical journals which have so kindly consented to quotations from their articles.

FREDERICK C. SMITH.

Foreword

FROM time to time discoveries are made which are epochal in nature, exerting a far-reaching influence on medical practice. The discovery of the sulfa drugs was an event of this nature. With their advent a whole group of infections—notably those due to the pneumococci and certain forms of streptococci—came under reasonable control for the first time.

Since the appearance of sulfanilamide a host of biochemists and other scientific workers have been engaged in bringing out successive and improved types of sulfa preparations. Each new product has increased the general usefulness of the sulfa preparations, until now many infections are being successfully treated, which only a few years ago were almost invariably fatal.

The tremendous interest that the sulfa drugs have aroused has been productive of an enormous volume of literature dealing with various aspects of the subject. Many of the contributions have been thoughtfully prepared and scientifically controlled. Others, again, have set forth conclusions too often premature and not based upon careful investigative procedures. It is timely, therefore, that someone possessing a critical point of view should analyze the current literature on the sulfa drugs and present in a systematic way the practical results of this great volume of investigation.

Dr. Smith has undertaken such a task, the result of which is this volume. It represents the painstaking and critical analysis of our present knowledge of the sulfa preparations. An enormous amount of data has been sifted and the conclusions should prove unusually worthwhile to those who are engaged in the practice of medicine.

As is the case with all active preparations, the sulfa drugs, although capable of almost unbelievable good, are not without

their dangers. The toxic effects of these drugs, which in a number of instances have proved fatal, have not been sufficiently stressed and are often overlooked by those who use sulfa drugs heedlessly. In this volume, both the dangers of the sulfa drugs, as well as the particular indications for their use, are stressed, so that any thoughtful reader should be able to obtain a good idea of the uses and abuses of these justly popular but potent therapeutic agents.

The author is to be congratulated upon making available to the medical profession such a well-considered review of this much discussed but often poorly understood subject.

GEORGE MORRIS PIERSOL, M.D.

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Part I



General Information Concerning the Sulfonamides

Introduction

CHEMOTHERAPY with the sulfonamide drugs, the so-called sulfa drugs, has been hailed by many as the greatest advance ever made in Medicine. Whether one concedes that this is *the* greatest advance might be open to question, for certainly the divorcing of Medicine from the sorcery and witchcraft of the Middle Ages, the discovery of the circulation of the blood by Harvey, the introduction of general anesthesia into surgery by Morton, the discovery of insulin by Banting, and many other milestones in medical history all have been great advances. None the less, sulfonamide therapy ranks high among medical discoveries and may easily constitute one reason for making the 20th Century an era to be remembered for ages to come.

The sulfonamides are saving thousands of lives that formerly were lost and much morbidity is being eliminated by them, but these very properties of the drugs bring new problems to the practice of medicine. The drugs cannot safely be administered in a hit-or-miss manner any more than can other potent remedies. Their very potency bespeaks toxic properties, some of them being more toxic than others, and, in fact, often the margin of safety between therapeutic effect and toxic reaction is not very great. The result of this is that the patient receiving sulfonamide therapy must be kept under a closer medical supervision than with most other remedies.

Many have felt that the range of effectiveness of the sulfonamides is so great that much of the burden of diagnosis has been eliminated, that in effect they constitute a cure-all. Far from this being the case, even though any member of the sulfonamide group may strike at the cause of several different diseases, accurate diagnosis remains just as important as ever, and sometimes even more so. Sulfapyridine, for example, is an effective

agent against pneumococcal pneumonia, but neither it nor any other sulfa drug has any effect against virus pneumonia nor against influenzal pneumonia. Pneumonia is a rapidly killing disease with a very high mortality rate, and if one is satisfied in knowing that pneumonia is present without knowing the *kind* of pneumonia and depends upon sulfa drugs in every case of pneumonia, he will condemn many too trustful patients to untimely graves.

Neither do the sulfa drugs lend themselves to self-medication by the laity, although articles have appeared in magazines which gave the impression that sulfonamides have eliminated the need for medical supervision. Writing on this subject editorially,¹ the author made the following comments:

The dangers of self-medication by the laity have been stressed from time immemorial by the medical profession, but the popularity and widespread use of the sulfonamides make such warnings more important than ever. A popular lay writer some months ago proclaimed that gonorrhea is now conquered and all one has to do is take a few cents worth of sulfathiazole. A lady recently called the writer and said her husband had had a diagnosis of pneumonia but refused to go to bed or get medical attention and would it be all right to give him sulfapyridine. A cartoon not long ago depicted an African "medicine man" and the caption had him saying that he did not feel like going into his dance so would give sulfanilamide instead.

Everyone knows about the sulfonamides and most lay persons have the idea that their powers are limitless and that one can cure himself of practically anything with a handful of tablets. The corollary is obvious. If the sulfonamides are such a cure-all and so easily obtainable, why bother to spend money for a medical diagnosis? Since the doctor will prescribe a sulfonamide anyhow, one might just as well go immediately to the corner drug store and be cured for a total expenditure of but a few cents.

Unfortunately for the misguided individuals with such a mistaken viewpoint, nowhere is the art of medicine called into play

so much as in the use of the sulfonamides. A teacher of materia medica and therapeutics many years ago was wont to emphasize to each of his classes that a drug without toxic manifestations was probably without therapeutic action. The therapeutic effects of the sulfonamides are often truly amazing and so, too, can their toxic reactions be severe. In fact, the margin of safety between therapeutic effect and toxicity sometimes is slim and the doctor must be ever alert to detect the stage at which unwanted effects begin. In an English book on therapeutics which was published a year or more ago, the author stated that the sulfonamides should be given only while the patient was under strict supervision by his physician in a hospital, or at least in bed. Such caution is exaggerated but it does give force to the fact that promiscuous and thoughtless use of the sulfonamides is inexcusable. Certainly, it teaches that self-medication with such potent remedies only invites trouble.

The frequency of some of the toxic reactions following the administration of the sulfonamides is worthy of note. Nausea and/or vomiting occurs in the following percentages: Sulfanilamide, 10 to 20; sulfapyridine, 40 to 55; sulfathiazole, 23 to 40, sulfaguanidine, 2 to 5, and sulfadiazine, 5 to 9. Fever: Sulfanilamide, 10; sulfapyridine, 2 to 5; sulfathiazole, 5 to 6, and sulfadiazine, 1. Anemia: Sulfanilamide, 1 to 2, and sulfapyridine, 2 to 3. Leukopenia: Sulfanilamide, 0.1; sulfapyridine, 0.1 to 0.5, and sulfadiazine, 2. Hematuria: Sulfapyridine, 2 to 3; sulfathiazole, 2 to 3, and sulfadiazine, 0.5 to 1. Oliguria occurs in a small percentage of cases receiving sulfapyridine, sulfathiazole, or sulfadiazine; jaundice and hepatitis occur rarely after the administration of sulfanilamide or sulfathiazole. In summary, the serious toxic manifestations of sulfanilamide are acute hemolytic anemia, leukopenia, and liver damage. Sulfathiazole and sulfapyridine cause nausea, vomiting, and renal irritation more often than the other sulfonamides, although the vomiting is less severe and less frequent following the use of sulfathiazole.

Furthermore, the sulfonamides are not a cure all, as so many of the laity seem to think. Among the diseases not influenced

by sulfonamide therapy are the common cold, epidemic influenza, infectious mononucleosis, rheumatic fever (except in prophylaxis), poliomyelitis, spirochetal disease, trichinosis, tuberculosis, rabies, bronchopneumonia, and rickettsial disease. A few cases of subacute bacterial endocarditis are said to have been cleared up with sulfonamides, but generally they are believed valueless in this disease. These drugs are incapable of neutralizing the soluble toxin of the hemolytic streptococcus and therefore have no effect on the eruption of scarlet fever. Accordingly, persons receiving sulfonamides for the aforementioned diseases cannot receive any benefit, but are subjected to the dangers of toxic reaction.

Like all new therapeutic procedures, be they new drugs, new forms of physical therapy, or some other new kind of treatment, there is at first a period of wild enthusiasm for what the therapy can accomplish. Back about 1912, for instance, there were many who believed that a single injection of salvarsan (arsphenamine) would cure syphilis. Then, as clinical experience with a new procedure grows and clinical reports accumulate, the limitations of the procedure begin to be appreciated until finally, if it weathers the usage of time, it is applied with as near an approach to scientific exactness as is possible in a science with so many variables. The sulfonamides are almost in this final stage. They have been one of the greatest advances in medicine of the present century. Nonetheless, the more we learn of them, the more we know that their use can never be haphazard and without careful study of the patient. Certainly, they lend themselves least of all drugs in materia medica to self-medication.

Spink,² under the title "The Use and Abuse of Chemotherapy," warns against the promiscuous and inconsidered use of the sulfonamide drugs, particularly in respiratory infections.

The sulfonamide compounds are effective in the treatment of many bacterial infections. While very satisfactory results have been obtained in the treatment of certain types of pneumonia, I should like to discuss briefly with you some of the uses and abuses of sulfonamide therapy in upper respiratory tract infec-

the past year, sulfadiazine has been used in the treatment of these patients with satisfactory results. The therapeutic response has been by no means dramatic, but many of the patients feel and look better coincident with the use of sulfadiazine.

Acute tracheobronchitis may be due to different biological agents. I have been reluctant to use the sulfonamide compounds for this condition, but some of my associates have insisted upon a trial of sulfadiazine not only in their patients, but when they themselves were the patients. Coincident with the administration of suldiadiazine, improvement in the condition of the patient has frequently been apparent. The doses used were approximately those prescribed for patients with pneumonia. We have not been favorably impressed by the results of chemotherapy in patients having chronic bronchitis.

Influenza is a loosely used term. Epidemic influenza is due to a specific virus, and chemotherapy is without effect in experimentally induced infections in the lower animals. Likewise, sulfonamide therapy is not effective in proved human cases of epidemic influenza. As Finland and his associates have pointed out, sulfathiazole and sulfadiazine have been of considerable value in secondary pulmonary infections due to the staphylococcus in patients from whom the influenza virus was also isolated. It is not at all unlikely that sulfonamide therapy may be beneficial for prophylactic purposes when epidemic influenza occurs in a community in association with a high incidence of pulmonary complications.

During the past few years physicians in various parts of the Country have encountered many cases of atypical pneumonia of doubtful etiology, and often called virus pneumonia. Many physicians in Minnesota have encountered such cases. The general impression is that the sulfonamides are not very effective therapeutically or prophylactically. However, it is my policy to administer a sulfonamide, usually sulfadiazine, to every patient having evidence of pneumonia. Full therapeutic doses are given for at least 48 hours. If, at the end of this time, the biological cause of the infection has not been defined, and the patient shows

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no improvement, chemotherapy is discontinued. In a few instances, where we have not been able to make a bacteriological diagnosis, the patients have responded quite well following sulfonamide therapy. It is possible that these cases represented pneumococcal infections, although we were unable to isolate pneumococci.

In conclusion, I would like to emphasize that the availability of the sulfonamides has marked a tremendous advancement in our therapy of pneumonia and its complications. The promiscuous use of these drugs for mild respiratory infections of doubtful etiology has afforded questionable therapeutic results, and has provoked many instances of hypersensitivity to the compounds. The medical profession must assume a more critical and conservative attitude for the present in this type of therapy. This must be done in order to correct the present attitude of many lay people, who have been led to believe that sulfonamide therapy is an established and harmless procedure in the management of respiratory infections.

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1. SMITH, F. C.: *Med. World* 61:115 (March) 1913.
2. SPRINK, W. W.: *Minnesota Med.* 25 988 (Dec) 1942.

Pharmacology and Therapeutics

EHRLICH'S dream of a chemotherapeutic agent highly toxic to pathogenic organisms while innocuous to the human organism seems to have approached fruition in the group of drugs known as the sulfonamides. The drugs are far from being harmless; in fact, sulfanilamide, sulfapyridine, and sulfathiazole can be highly toxic, and the newer members of the group are less toxic, but still capable of doing harm if handled without intelligence. However, the therapeutic value of the entire group is now well established, and sulfonamide therapy can well be said to be one of the great advances in the history of Medicine.

If one is to obtain the maximum of success with the sulfonamide drugs, it is very important that he have a complete understanding of the factors which make for success or failure in the treatment of different types of infection. The first of these requisites is the proper selection of drug. Clinical trial has shown that certain bacteria are more sensitive than others to the various members of the group. Therefore, for a particular disease, one should select the sulfonamide known to be most effective from clinical experience. The word "clinical" is emphasized because a number of sulfonamide drugs have shown a high degree of antibacterial activity against many kinds of experimental infections, but because of their behavior and toxicity in man only a few of these compounds are of clinical usefulness.

Sulfanilamide is the one drug of the group which has solubility as a characteristic; the others have little solubility in water, although they attain greater solubility in body fluids. However, certain salts of the drugs have been introduced for parenteral use. The drug concentration reached locally and in the blood depends both upon the rate of entry into and the rate of exit from the local area and the circulating blood.

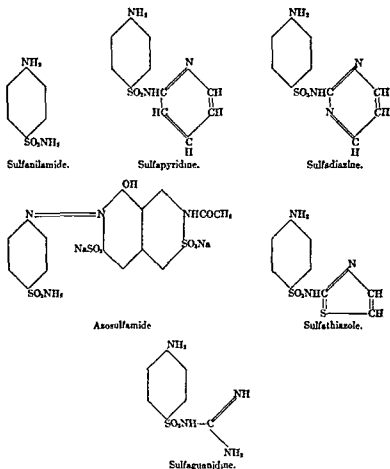


Fig 1—Structural formulas of sulfonamide compounds.

The rationale for the local use of the sulfonamides is the higher concentration thus obtained locally. Also, since sulfanilamide has greater solubility in body fluids, its local use has proved most satisfactory. Against this greater solubility of sulfanilamide, however, the limited solubility of sulfapyridine, sulfathiazole, and sulfadiazine permits these drugs to remain longer in the wound and thus give a longer-lasting action.

Given by mouth, the sulfonamide drugs mentioned above are almost completely absorbed from the intestinal tract into the

TABLE 1—COMPARISON OF THE ABSORPTION, EXCRETION, AND TOXICITY, AND THE BACTERIOSTATIC ACTIVITY OF SULFANILAMIDE AND A SERIES OF ITS DERIVATIVES, AS INDICATED BY THE LOCAL EFFECTS ON THE COLIFORM BACTERIA IN THE BOWEL OF THE DOG

Compounds	Total Daily Dose, Gm. per kg.		Concentration of the Drug in the Blood, mg. per 100 cc.		Concentration of the Drug in the Urine, mg. per 100 cc.		Drug Concentration of the Stool (Gm. per 100 cc. Based on 11 after Content of Feces)	Comparative Antibacterial Action	Toxicity	Comments
	Daily Dose	Dose, Gm. per kg.	Free	Conjugated	Free	Conjugated				
Sulfanilic acid	2	15	180	220			Saturated	±	++	Readily absorbed, giving high blood levels with relatively little effect on coliform organisms in bowel
	2	10	100	100			Saturated	±	++	
Sulfanilamide	6	0.25	120				0.55	++	0	Some effect on coliform bacteria, but not sufficient even at toxic levels of drug.
	6	0.5	300				0.60	++	0	
	6	1.0	500					++	+++	
Sulfadiazine	6	1.0	450				0.21	++	++	Local action insignificant in dosages causing toxic manifestations.
Sulfathiazole	6	0.25	150		Crystals			0	+	High blood levels of drug without local action
Sulfanilyguanidine	6	0.3	50		..		50	++	0	1 Gm. per kg. per day in six equally divided doses causes moderate drop in coliform organisms in bowel; concentration of drug in blood moderately high; urine saturated; toxic manifestations severe in a large percentage of animals with occurrence of corneal lesions
	6	1.0	10 to 15		Saturated crystals		Solid drug	++	+++	
	2	5.0	10 to 15		Saturated crystals		Solid drug	++	+++	
	5	5.0	10 to 35		Saturated crystals		Solid drug	++	+++	
Maleylsulfanilamide	6	0.25	2	20		500		±	+++	Highly toxic, producing anorexia, diarrhea, vomiting, paralysis and death; death may occur after few days; with small doses animals become paralyzed and die weeks after discontinuance of drug.
	6	0.5	3	30		600		+++	+++	
	6	1.0						+++	+++	
Maleylsulfanilydrosimide	2	5.0						+++	+++	Highly toxic, causing vomiting, bloody diarrhea, nephritis and death

TABLE 1—Continued

Compounds	Daily Dose, gm per 100 cc	Concentration of the Drug in the Blood, mg per 100 cc		Concentration of the Drug in the Urine, mg per 100 cc		Drug Concentration of the Stool (Gm per 100 cc Based on Water Content of Feces)	Com- parative Antibacterial Action	Toxicity	Comments
		Free	Conjugated	Free	Conjugated				
Succinylsulfanilamide	0.25	2.5	16	210	960	5.0	+	0	Low toxicity; anorexia and vomiting occur with higher dosage levels, causes no deaths, all animals recover immediately after dosage is lowered, high antibacterial activity; animals healthy after seven weeks' dosage of 1 Gm per kg. daily, no tissue lesions occur.
	0.5	2.5	1.0	350	2,400	5.0	++	0	
	1.0	4.0	1.5			5.0	+++	0	
	2.0	2.5	1.5			4.0	++++	++	
	5.0	2.5	0.5				++++	++	
Succinylsulfanilamide and sulfanilamide	0.25*	2.5	0			2.5	++	0	Action of succinylsulfanilamide somewhat enhanced by simultaneous administration of sulfanilamide
	0.25†	2.5	0						
	0.5*	2.5	2.5			5.0	+++	0	
	0.25†								
Succinylsulfanilamide and sulfadiazine	0.5	45	4.0			8.0	+++	0	Simultaneous administration of sulfadiazine with succinylsulfanilamide enhances activity of latter, blood concentration becomes rather elevated.
	0.5								
Succinylsulfanilylhydrazide	0.5						++	+++	Extremely toxic, causing bloody diarrhea and extensive gastroenteritis.
	0.5						0	++++	
Succinylsulfathiazole	0.05	2	4	65	170	5.0	+	0	Low toxicity; only toxic manifestation observed was anorexia after high dosages, animals receiving 1 Gm per kg. daily for five weeks showed no evidence of toxicity, during this entire period coliform bacteria were at extremely low levels, extensive tissue studies revealed no abnormalities
	0.1	3	5	80	270	4.0	++	0	
	0.25	4	4	125	560	6.0	++	0	
	0.5	3	4	180	600	5.0	+++	0	
	1.0	3.5	5	360	600	5.0	++++	0	
	2.0	3.5	7	250	600	5.0	++++	+	

TABLE 1—Continued

Sulfathiazole and succinylsulfathiazole	6	0.25†	11.4	0.4		5.3	++	+	Simultaneous administration of sulfathiazole with succinylsulfathiazole augments effect on coliform organisms in bowel (chart 5); some toxicity due to relatively high con- centration of sulfathiazole in blood
	6	0.10‡							
	6	0.25‡	13.2	1.83		6.0	+++	+	
	6	0.25‡							
	6	0.25‡	12.0	1.4		6.5	++++	+	
	6	0.50§							
Succinylsulfanilamide- ethylthiazolidone	6	0.5		6			+++	+++	Moderately toxic; anorexia develops by third day, compound has fair degree of antibac- terial activity.
	6	1.0		10			+++	+++	
	6	2.0		4	220	5.0	++	+++	
Succinylsulfapyridine	6	0.5		4			+++	+++	While this drug has moderate antibacterial activity, it is too toxic for large doses
	6	1.0		33	1,305	3.7	+++	+++	Too toxic at doses having antibacterial ac- tivity.
Succinylsulfadiazine	6	0.5					++	++	
	6	1.0					+++	+++	
	6	2.0					+++	+++	
Succinylsulfanilyl- guanidine	6	0.05					0	0	While this drug has exhibited no toxicity under the conditions studied, it does not appear to be a satisfactory compound, be- cause even though it promptly reduces the coliform count, it fails to keep the count down, after a week the effect completely disappears
	6	0.10					0	0	
	6	0.25					0	0	
	6	0.50					+++(1)	0	
	6	1.0					+++(1)	0	
Succinylsulfamethyl- diazine	6	0.5					+	0	Low toxicity, antibacterial activity not pro- nounced
	6	1.0					++	0	

* Succinylsulfanilamide
† Sulfanilamide

‡ Sulfathiazole
§ Succinylsulfathiazole

(Poth, E. J.; Kneets, F. L.; Lee, J. T., and Inoué, F. *Arch Surg.*)

blood stream within two to four hours after the ingestion of from 1- to 3-Gm. doses. After the fourth hour, with the exception of sulfadiazine, the amount of drug in the circulating blood diminishes rapidly, so that it is necessary to administer a large initial dose and to follow this with doses given at four-hour intervals night and day. If given by parenteral routes blood concentrations, obviously, are reached much more rapidly.

TABLE 2—PHARMACOLOGIC PROPERTIES OF THE SULFONAMIDES

<i>Water Solubility at Room Temperature</i>	<i>Sulfanilamide</i>	<i>Sulfapyridine</i>	<i>Sulfathiazole</i>	<i>Sulfadiazine</i>	<i>Sulfaguanidine</i>
	<i>1 per cent</i>	<i>0.03 per cent</i>	<i>0.1 per cent</i>	<i>0.01 per cent</i>	<i>0.2 per cent</i>
Absorption	Good	Fair but irregular	Good	Good	Poor
Excretion	Good	Good	Good (rapid)	Good (slow)	Good
Acetylation	Slight 10 to 15 per cent	Great* 15 to 75 per cent	Slight* 0 to 30 per cent	Slight**	Moderate
<i>Diffusion in fluid and tissue</i>	Good	Good	Fair***	Good	Fair***
Toxicity	Moderate	Greater than moderate	Less than moderate	Mild	Mild
Bacteriostatic effect	Monovalent, hemolytic streptococci	Polyvalent, hemolytic streptococci, pneumococci, staphylococci			Intestinal bacterial infections

*Compound insoluble, **Compound soluble, ***Poor in cerebrospinal fluid

Following absorption into the blood stream the sulfonamides are partially conjugated by the liver into acetylated forms, which are therapeutically inactive but highly toxic. This acetylation takes up approximately the following percentages of the drugs: Sulfanilamide, 20 per cent; sulfathiazole, 30 per cent, and sulfadiazine, 15 per cent. Sulfapyridine has a very irregular conjugation, varying from 10 to 90 per cent, with an average of about 30 per cent, which has greatly limited its usefulness.

After passing into the blood stream the sulfonamides are uniformly distributed throughout the body, the concentration in various tissues being dependent upon their vascularity. All are

present in exudates and transudates in higher concentrations than in the blood stream. With the exception of sulfathiazole they pass readily into the cerebrospinal fluid in concentrations averaging 50 to 65 per cent of that present in the blood. Sulfathiazole, however, reaches a concentration of only about 20 per

TABLE 3—DISEASES FAVORABLY INFLUENCED BY
SULFONAMIDE COMPOUNDS

<i>Sulfanilamide</i>	<i>Sulfapyridine</i>	<i>Sulfathiazole</i>	<i>Sulfadiazine</i>
Hemolytic streptococcal infections	Pneumococcal infections	Pneumococcal infections	Pneumococcal infections
Abscesses	Pneumonia	Pneumonia	Pneumonia
Adenitis	Meningitis		
Cellulitis	Otitis Media		
Erysipelas	Peritonitis		
Lymphangitis	Sinusitis (acute)		
Mastoiditis	Gonococcal infections	Gonococcal infections	Gonococcal infections
Meningitis	Arthritis	Arthritis	
Osteomyelitis	Gonorrhea	Male gonorrhea	
Otitis media	Ophthalmia	Staphylococcal infections	Meningococcal meningitis
Peritonitis		Carbuncle	Erysipelas
Peritonsillar abscess		Cellulitis	
Puerperal sepsis		Septicemia	
Septicemia		Urinary tract infections	Acute urinary tract infections
Ulcers		A. aerogenes	
Meningococcal infections		B. pyocyaneus	
Meningitis		E. coli	
Septicemia		S. albus	
Urinary tract infections		S. aureus	
Lymphogranuloma venereum			

(Reimann's Treatment in General Medicine, F. A. Davis Co., Publishers.)

cent of that in the blood, limiting its usefulness in meningeal infections. The good results which have been reported in meningitis from sulfathiazole have been due to the fact that the antibacterial concentrations of the drug in submeningeal tissues curtail bacterial invasion and probably limit the spread of

TABLE 4—DISEASES IN WHICH SULFONAMIDE COMPOUNDS
ARE OF DOUBTFUL VALUE

<i>Sulfanilamide</i>	<i>Sulfapyridine</i>	<i>Sulfathiazole</i>	<i>Sulfaguanidine</i>
Actinomycosis	Brucella infections	Ulcerative colitis	Bacillary dysentery*
Brucella infections	Friedlander's bacillus in- fections	E. coli infections	
Hemolytic strepto- coccal infections (Lancefield)	Pemphigus	Staphylococcal pneumonia	Ulcerative colitis
Groups B & C	Streptococcus veridans	Actinomycosis	
Hemolytic strepto- coccus pneumonia or empyema	Subacute bac- terial endo- carditis	Pneumococcal mastoiditis	
Influenza bacillus meningitis	Ulcerative colitis		
Streptococcus veridans	B influenza meningitis		
Subacute bacterial endocarditis	Actinomycosis		
Ulcerative colitis	Gonococcal endocarditis		
Trachoma			
Gas gangrene (Clos. welchii)			
B. proteus infection			

*See section on Bacillary Dysentery

(Reimann's *Treatments in General Medicine*, F. A. Davis Co., Publishers)

the process as much as the drug in the spinal fluid itself. Nevertheless, the direct action of the drug in the spinal fluid is important, so that sulfonamides other than sulfathiazole should be used in meningitis.

The sulfonamide drugs, with the exception of sulfathiazole, readily penetrate the red blood cells. This is of clinical importance in the development of hemolytic anemia.

All of the sulfonamide drugs, regardless of their route of administration, are excreted in the urine both in their free and in their acetylated form. With the exception of sulfadiazine, excretion from the body is complete within 24 hours. The kidneys excrete the drugs in a manner similar to urea, but reabsorption by the tubules occurs to a greater extent and elimina-

TABLE 5—DISEASES IN WHICH THE SULFONAMIDE COMPOUNDS
AVAILABLE AT PRESENT ARE INEFFECTIVE

<i>Sulfanilamide</i>	<i>Sulfapyridine</i>	<i>Sulfathiazole</i>
Anaerobic streptococcal infections	Anaerobic streptococcal infections	Anaerobic streptococcal infections
Nonhemolytic streptococcal infections	Common colds	Influenza
<i>Streptococcus veridans</i> infection	Influenza and influenza-like infections	Typhoid
Bacillary dysentery	Paratyphoid fever	Pneumococcal empyema, arthritis, endocarditis
Common colds	Chronic sinusitis	"Virus" pneumonia
Influenza and influenza-like infections	Tularemia	Focal purulent infections
Rheumatic fever (acute)	Typhoid	Subacute bacterial endocarditis
Rocky Mountain spotted fever	"Virus" pneumonia	
Typhus fever	Focal purulent infections	
Chronic sinusitis	Subacute bacterial endocarditis	
<i>Trichomonas vaginalis</i> infections		
Tuberculosis		
Tularemia		
Typhoid fever		
Paratyphoid fever		
Anthrax		
Torulosis		
Malaria		

(Reimann's *Treatment in General Medicine*, F. A. Davis Co., Publishers.)

tion is reduced by kidney damage. The clearance of the drugs is increased by increasing the flow of urine, and this is best obtained by forcing fluids, even parenterally, if necessary. A decrease in the output of urine encourages the deposit of the drug crystals and the formation of stones. Hence, it is extremely important that urinary output be maintained at not less than 1200 cc. daily. This problem becomes more acute in hot climates, where sweating greatly decreases urinary output. See section on Gonorrhea.

Chemotherapy, to be effective, necessitates the administration of the drug in such a manner as to achieve a sufficient concentra-

TABLE 6—CONDITIONS FOR WHICH SULFONAMIDE COMPOUNDS
MAY BE OF VALUE IN PROPHYLAXIS

<i>Sulfanilamide</i>	<i>Sulfapyridine</i>	<i>Sulfathiazole</i>
Burns Compound fractures Hemolytic streptococcal sequels to scarlet fever Extensive tissue injuries Accidental Operative Gunshot wounds Otitis media Peritonitis (appendec- tomies, large bowel resections, etc) Rheumatic fever	Otitis media*	Burns Peritonitis (appendec- tomies, large bowel restrictions, etc.) Urinary tract infections (Urological operations)

*See section on Otitis Media

(Reimann's *Treatment in General Medicine*, F. A. Davis Co., Publishers.)

tion in the circulating blood or/and at the site of the infection, and to maintain the concentration until the patient acquires enough immunity to prevent a relapse. Generally, the oral administration is the most satisfactory in the treatment of systemic infections. When it is necessary to obtain maximum concentration quickly or when there is some contraindication to oral therapy, the drug may be given parenterally, and in this case, because of its greater solubility in water, sulfanilamide is usually the drug of choice. Parenteral administration of sulfanilamide can be by vein or subcutaneously as an 0.8 per cent solution in sterile physiological salt solution. When it is desired to administer sulfapyridine, sulfathiazole, or sulfadiazine parenterally it is necessary to use the sodium salts of these drugs. Usually they are given as a five per cent solution in sterile distilled water and are administered intravenously. Sulfadiazine, because of its slower excretion, has given more satisfactory results when used intravenously than have sulfapyridine or sulfathiazole.

Placental Transmission of Sulfonamides: Sulfanilamide, sulfathiazole, and sulfadiazine diffuse readily across the placenta.

TABLE 7

Observation	Sulfa- sulfamide	Sulfa- pyridine	Sulfa- thiazole	Sulfa- diamine	Sulfa- guanidine
Solubility in water	Pure drug 0.8-1.0% Neopronto- sil 5%	Pure drug 0.1% Sodium salt 75%	Pure drug 0.09-0.6% Sodium salt 5-20%	Pure drug 0.0123% Sodium salt 5%	Pure drug 0.22%
Intravenous solution	Not indicated	5% in distilled water	1% in distilled water	5% in saline or distilled water	
Subcutaneous solution	0.8-1% in saline	0.3-0.7% in saline	0.5% in distilled water and 5% glucose	0.3-0.8% in saline	
Intramuscular solution	5%	10 or 33½%			
Absorption Peak of blood level after single oral dose	4 hours	6 hours	4 hours or less	6 hours	
Dependability	Uniform	Erratic but sodium salt readily absorbed	Sodium salt absorbed almost im- mediately	Sodium salt absorbed almost im- mediately	Only small amounts absorbed
Rectal or lower colon administration	1% sol. well absorbed	Poorly absorbed Not advised	Poorly absorbed Not advised	Poorly absorbed Not advised	Poorly absorbed Not advised
Local application Order of ef- fectiveness based on solubility at 37° C.	1,500	61	184	124	61
Renal excretion	Rather rapid	Variable	Very rapid	Slow	
Ease in maintaining adequate blood level because of excretion	Easy	Variable	Difficult	Easy	
Acetylation in blood	10-15%	15-75%*	0-30%**	Small amounts	?
In urine	50%	Over 50%	Small amounts	33%	30%
Solubility of acetylsulfonamide in urine	Very soluble	Slightly soluble	Slightly soluble	Very soluble	Slightly soluble
Clinical urinary concretions	0	+++	++	+	?

* Acetylation of sodium sulfapyridine is distinctly less than that of sulfapyridine.

** Sulfathiazole is apparently excreted so rapidly that the liver cannot acetylate it.

TABLE 7—Continued

Observation	Sulfa- nilamide	Sulfa- pyridine	Sulfa- thiazole	Sulfa- diazine	Sulfa- guanidine
Presence of sulfonamides in body tissues and fluids where dif- ference exists Bile and gallbladder	Concen- trated	Concen- trated	Concen- trated		
Cerebrospinal fluid	Present	Present	Present		
Liver and kidney	Present	Present in great content	Present	Present	Present if absorbed
Pleural, pericardial and peritoneal fluid	Present	Present	Present	Present	Present if absorbed
Antipyretic effect	Active	Active	Active		

* Acetylation of sodium sulfapyridine is distinctly less than that of sulfapyridine

** Sulfathiazole is apparently excreted so rapidly that the liver cannot acetylate it

(Schnitzer, M. A. *Oxford Loose Leaf Medicine*)

A single intravenous dose of sodium sulfathiazole or sodium sulfadiazine given to a mother in labor will appear in the fetal blood almost immediately. The drugs are retained there in therapeutically effective concentrations for at least six hours in the case of sulfathiazole and considerably longer in the case of sulfadiazine. Equilibrium between the maternal and fetal blood is established within three hours. A higher concentration of sodium sulfadiazine is obtainable in the fetal blood than is possible with an equal dose of sulfathiazole. These drugs also appear in the amniotic fluid, but later than they do in the fetal blood.

Speert¹ uses this placental transmission of sulfonamides to treat the fetus prophylactically when the mother's genital tract harbors the gonococcus. He also recommends this form of intra-uterine treatment of the fetus in cases of intercurrent or intra-partum infection of the mother by susceptible organisms.

Dosage

The amount of drug necessary to obtain the desired therapeutic results depends upon a good many factors. The first

TABLE 8—SULFONAMIDE BLOOD CONCENTRATIONS OF THE FREE (NONACETYLATED) DRUG THAT ARE AT PRESENT CONSIDERED DESIRABLE

<i>Drug</i>	<i>Ordinary Infection</i>	<i>Critically Ill Patient</i>
Sulfanilamide.	8 to 10 mg. per 100 cc.	10 to 15 mg. per 100 cc.
Sulfapyridine	5 to 10 mg. per 100 cc.	10 to 15 mg. per 100 cc.
Sulfathiazole.	5 to 10 mg. per 100 cc.	10 to 15 mg. per 100 cc.
Sulfadiazine .	5 to 10 mg. per 100 cc.	10 to 15 mg. per 100 cc.

(*Physicians' Bulletin*, Eli Lilly and Co.)

consideration is the infecting organism. Different organisms have differing degrees of susceptibility to the drug and produce many degrees of severity as well as types of lesion. Other factors to be considered are the state of kidney function, the rate of drug absorption, and the state of dehydration. Also, acute conditions, particularly those involving soft tissues, require generally higher dosages than do chronic, long-standing ones, or infections involving the urinary tract.

It can be seen that definite rules of dosage to fit all cases cannot be given. Often with sulfanilamide it is necessary to watch the blood concentration and to maintain it at a concentration which general clinical experience has shown to be optimum for the particular type of infection. A drop in temperature can be deceptive and cessation of chemotherapy may be followed by a spread or recurrence of the infection. A rise in temperature, on the other hand, may be due to drug fever and not to an increase in exacerbation of the infection. Generally, it is a safe rule once chemotherapy has been started to continue the drug until complete clinical cure has been obtained. A safe procedure is gradually to decrease the dosage over a period of days, carefully watching the patient for any evidence of any recurrent infection.

Blood concentration, unfortunately, except with sulfanilamide, is no indication of the effectiveness of the drug. It is frequently noted that prompt recovery ensues with a low blood

TABLE 9

<i>Drug</i>	<i>Disease</i>	<i>Route</i>	<i>Initial Dose</i>	<i>Subsequent Doses</i>	<i>Duration of Treatment (except as toxic effects force earlier discontinuance)</i>
Sulfanilamide	Mild to moderately severe beta hemolytic streptococcal infections	Oral	0.1 Gm. per kg. (1 Gm. per 22 lb.) (0.7 gr. per lb.)	1/6 initial dose q. 4 h. day and night.	Continue until temperature is normal for 72 hours. Then taper off the dose.
Amps. Sulfanilamide 1% solution at 37° C. in saline or 1/6 molar sodium lactate solution	Meningococcal meningitis or severe hemolytic streptococcal infections	Parenteral (Hypodermoclysis)	10 cc. per kg. (100 cc. per 22 lb.) (600 cc. per 132 lb.)	1/4 initial dose q. 6 h. unless oral dosage becomes possible.	Continue until temperature is normal for 72 hours. Then taper off the dose.
Sulfapyridine	Pneumococcal pneumonia	Oral	4 Gm. with water	1 Gm. q. 4 h. Give adequate quantities of water.	Continue until temperature is normal for 72 hours. Then taper off the dose.
Sodium Sulfapyridine 5% solution	Pneumococcal meningitis	Intravenous	0.06 Gm. per kg. (12 cc. of 5% solution for each 22 lb.)	After 6 hours determine blood concentration. Give 1/6 of initial dose for each mg. percent rise in blood concentration desired. Substitute oral therapy if possible. Give large quantities of water.	Continue until patient shows signs of improvement and until two successive lumbar punctures are sterile. Watch for toxic effects. After this approximately 0.03 Gm. per kg. twice daily for several days.
Sulfathiazole	Pneumococcal pneumonia	Oral	4 Gm. with water	1 Gm. q. 4 h. day and night. Give adequate quantities of water. Alkalinize urine.	Continue until temperature is normal for 72 hours.
Sulfathiazole	Ordinary staphylococcal infections	Oral	4 Gm. with water	1 Gm. q. 4 h. day and night. Give adequate quantities of water. Alkalinize urine.	Continue for 5 to 7 days.
Sulfathiazole	Severe staphylococcal infections, cellulitis, lymphangitis, or acute osteomyelitis	Oral	4 Gm. with water	1.5 Gm. q. 4 h. day and night. Give large quantities of water. Alkalinize urine.	Continue as long as evidence of spreading of infection continues. Then reduce 1 Gm. q. 4 h. and continue as indicated.

TABLE 9—Continued

<i>Drug</i>	<i>Disease</i>	<i>Route</i>	<i>Initial Dose</i>	<i>Subsequent Doses</i>	<i>Duration of Treatment (except as toxic effects force earlier discontinuance)</i>
Sulfathiazole	Staphylococcal bacteremia	Oral	4 Gm with water	1.5 Gm q 4 h day and night. Give large quantities of water. Alkalinize urine.	Continue until temperature is normal for 48 hours. Then 1 Gm. q 4 h for 14 days more. Frequent leukocyte counts especially indicated in prolonged treatment.
Sodium Sulfathiazole 5% solution	Severe pneumococcal or staphylococcal infections	Intravenous	0.06 Gm per kg (12 cc per 22 lb). In critical case give 0.1 Gm per kg (20 cc per 22 lb)	After 6 hours determine blood concentration. Give 1/6 of initial dose for each mg percent rise in blood concentration desired. Give large quantities of water. Alkalinize urine.	Continue until oral administration is possible, and then proceed as described under oral administration
Sulfathiazole	Gonorrhea ambulant patient	Oral	1 Gm	1 Gm 3 or 4 times daily (preferably 4). A glass of water may be suggested with each half-gram tablet	Continue until evidences of gonorrheal discharge from urethra or cervix cease and other signs are improved. Then give 2 to 3 Gm. daily for a week
Sulfathiazole	Gonorrhea hospitalized patient	Oral	4 Gm with water	1 Gm q 4 h day and night. Alkalinize urine	Continue as above. Discontinue if no improvement in 5 to 7 days, and later repeat using artificial fever and sulfathiazole, or sulfadiazine if preferred.
Sulfadiazine	Pneumococcal pneumonia	Oral	4 Gm with water	1 Gm. q 4 h day and night. Give adequate water. Alkalinize urine	Continue until temperature is normal for 72 hours. Then drug may be stopped
Sulfadiazine	Severe pneumococcal hemolytic streptococcal and staphylococcal infections and meningococcal meningitis	Oral	0.1 Gm per kg. (11 Gm per 22 lb) with water	1 to 1.5 Gm. q 4 h. Large quantities of fluid. Alkalinize urine.	Continue until temperature is normal 5 to 7 days. Then either stop or continue with smaller doses (as with sulfathiazole) until recovery is assured.

(Physicians' Bulletin, Eli Lilly and Co.)

TABLE 10—INTRAVENOUS DOSAGE OF SULFONAMIDES
Dosage of Sodium Sulfapyridine, Sodium Sulfathiazole, or Sodium Sulfadiazine That Will Increase the Blood Concentration of the Drug by Approximately 1 mg. per 100 cc. (Multiply This Dose by the Number of Mgs. Per Cent Rise That Is Desired)

<i>Weight of Patient in Pounds</i>	<i>Weight of Patient in Kilograms</i>	<i>Dosage in cc. of a 5% Solution of the Sodium Salt</i>	<i>Dose of the Sodium Salt in Grams (0.01 Gm. per Kilogram)</i>
11 lb.	5 kg.	1 cc.	0.05 Gm.
22 lb.	10 kg.	2 cc.	0.1 Gm.
33 lb.	15 kg.	3 cc.	0.15 Gm.
44 lb.	20 kg.	4 cc.	0.2 Gm.
55 lb.	25 kg.	5 cc.	0.25 Gm.
66 lb.	30 kg.	6 cc.	0.3 Gm.
77 lb.	35 kg.	7 cc.	0.35 Gm.
88 lb.	40 kg.	8 cc.	0.4 Gm.
110 lb.	50 kg.	10 cc.	0.5 Gm.
132 lb.	60 kg.	12 cc.	0.6 Gm.
154 lb.	70 kg.	14 cc.	0.7 Gm.

(Physicians' Bulletin, Eli Lilly and Co.)

TABLE 11—SULFONAMIDES—USE IN ORDER OF CHOICE

<i>Staphylococcus</i>	<i>Hemolytic Streptococcus</i>	<i>Pneumococcus</i>	<i>Meningococcus</i>	<i>Gonococcus</i>
1. Sulfathiazole	1. Sulfadiazine	1. Sulfadiazine	1. Sulfadiazine	1. Sulfathiazole
2. Sulfadiazine	2. Sulfanilamide	2. Sulfathiazole	2. Sulfanilamide	2. Sulfapyridine
3. Sulfapyridine	3. Sulfathiazole	3. Sulfapyridine	3. Sodium Sulfapyridine	3. Sulfadiazine
4. Sulfanilamide	4. Sulfapyridine	4. Sulfanilamide	4. Sodium Sulfathiazole	4. Sulfanilamide

(Physicians' Bulletin, Eli Lilly and Co.)

concentration and many times the patient grows worse with a high blood concentration. Were the degree of blood concentration a sure indication to the effectiveness of the sulfonamide, it would be a great boon and give a scientific exactness to sulfonamide therapy nowhere else achieved in Medicine, but it is perhaps fortunate for most physicians that this is not so, for most

medical practice must be done at times and places where laboratory facilities are not available. Usually the physician will use the sulfonamides, as he uses other drugs, in the dosage and manner which general clinical experience dictates as the best for giving the desired results.

Sulfanilamide: A blood concentration of 10 mg. per cent of free sulfanilamide gives maximum therapeutic effectiveness in

TABLE 12—SULFANILAMIDE (P-AMINOBENZENE SULFONAMIDE)

Clinical Indications:

Diseases: Streptococcal septicemia and related diseases, brucellosis, meningococcic meningitis, gonorrhea, gas gangrene, actinomycosis, venereal lymphogranulomata.

Possible Prophylaxis: Burns, wounds, compound fractures, otitis media, Peritonitis.

Adults:

Initial Dose: 0.10 Gm. per kg. of body weight.

Maintenance Dose: 1.10 Gm. per kg. body weight divided into six doses and given day and night for seven days or more after the temperature has returned to normal.

Children:

Same as for adults.

Absorption from gastrointestinal tract is excellent.

Diffusion into body fluids is very good.

Excreted rapidly in the urine.

Toxicity:

Rather high percentage of toxic and side reactions.

(Maether, R. O.: *J. Missouri S. Med. Assn.*)

most of the infections susceptible to the drug. In meningeal infections and a few others a blood concentration of 15 mg. per cent is required. Adequate blood concentration usually is accomplished by an initial dose of 3 to 5 Gm. of sulfonamide followed by 1 to 3 Gm. of the drug every four hours day and night. Locally sulfanilamide is used in a dosage of 1 Gm. for each ten square inches of surface involved, but in closed cavities not more than 5 Gm. should be used. At no time should more than 15 Gm. be used locally, for the drug is absorbed rapidly and toxic reactions can readily develop.

Sulfapyridine and Sulfathiazole: As previously mentioned, the blood concentration of sulfapyridine and sulfathiazole is of little significance. A blood level of 5 mg. per cent should be adequate in practically all cases except meningitis, where therapeutic results require blood levels of 10 to 15 mg. per cent. The initial dose of these two drugs usually is 3 or 4 Gm. and this is followed by 1 Gm. every four hours night and day. Intravenously the initial dose is the same and is followed by 2 Gm. every six hours night and day. Locally they are used the same as sulfanilamide, but their lesser solubility makes them less effective.

TABLE 13—SULFAPYRIDINE (2 (PARAAMINOBENZENE SULFONAMIDE) PYRIDINE)

Clinical Indications:

Diseases: Anthrax, strep. viridans meningitis pneumonia, meningitis, gonorrhea, brucellosis, trachoma, venereal lymphogranulomata.

Prophylaxis: Otitis media.

Dosage:

Adults:

Initial Dose: 4 Gm

Maintenance Dose: 1 Gm. every four hours day and night.

Blood level desired, 6 to 8 mg. per 100 cc. Continue until temperature has been normal for three days.

Children:

Initial Dose: 0.15 Gm. per kg. to 25 kg.

Maintenance Dose: 0.15 Gm. per kg. divided into four doses and given at six-hour intervals

Absorption from the gastrointestinal tract is good but erratic.

Diffusion into the body fluids is good. May reach 65 per cent of the blood concentration in the spinal fluid.

Excretion in urine is somewhat slower than with sulfanilamide, concentrations are likely to occur, particularly in acid urine.

Toxicity:

Considerably greater than with sulfanilamide.

(Muehrer, R. O. J. Missouri S. Med. Assn.)

Sulfadiazine: A blood level of 5 to 10 mg. per cent of free sulfadiazine will be effective in most infections which respond to this drug. This level can be achieved as a rule with an initial dose of 3 to 4 Gm. orally, followed by 1 Gm. every six hours night

TABLE 14—SULFATHIAZOLE (2 (PARAAMINOBENZENE SULFONAMIDE) THIAZOLE)

Clinical Indications:

Diseases: Pneumococcal infections in all forms, gonorrhea including gonococcal arthritis, staphylococcal infections of all types, colon bacillus infection of the urinary tract as well as the tissues.

Prophylaxis: Burns, genitourinary tract infections, peritonitis, and otitis media.

Adults:

Initial Dose: 4 Gm.

Maintenance Dose: 1 to 1.5 Gm. every four hours day and night. Should be continued for long periods, and particularly in staphylococcal infections.

Children:

Initial Dose: 0.15 Gm. per kg. body weight.

Maintenance Dose: 0.15 Gm. per kg. divided into six daily doses.

Absorption from the gastrointestinal tract is good.

Diffusion into the body fluids is good except for the spinal fluid in which concentration is fairly low.

Urinary excretion is rapid, concretions may form if urine output falls below 1000 cc. per 24 hours.

Toxicity:

Less than sulfanilamide, tends to cause fever and skin rashes

(Muether, R. O. *J. Missouri S. Med. Assn.*)

and day. Sometimes it may be necessary to give the drug at four-hour intervals to attain a higher blood level in some infections. Intravenously, using the sodium salt, it often is necessary to administer the drug only at 12-hour intervals.

Sulfaguanidine: This sulfonamide can be given by mouth in dosages high enough to give saturation of the intestinal tract without producing levels of the drug in the blood higher than 4 mg. per cent. This fact, combined with its antibacterial action, makes the drug particularly effective against such diseases as bacillary dysentery. Its administration is attended with very few toxic reactions, although drug rash, drug fever, conjunctivitis, and crystalluria have been reported. The initial dose is 0.1 Gm. per kg. of body weight, followed by 0.05 Gm. per kg. of body weight every four hours until the number of stools per day is five or less. See section on Bacillary Dysentery.

TABLE 15—SULFADIAZINE (2 (PARAAMINOBENZENE SULFONAMIDE)
PYRIDINE)

Clinical Indications:

Betastreptococcal infections of all types.

Pneumonococcal infections of all kinds.

Gonorrhea, meningococcus meningitis.

Staphylococcal infections, particularly osteomyelitis, sepsis, furunculosis, and impetigo.

Possible Prophylaxis: Burns, otitis media, peritonitis, and scarlet fever contacts.

Dosage

Adults

Initial Dose 0.1 Gm. per kg. body weight, usually 4 to 6 Gm.

Maintenance Dose: 1 Gm. every four to six hours until temperature has been normal for from 72 to 96 hours.

Children:

Same as for adults based on weight.

Absorption from the gastrointestinal tract is very good.

Diffusion into the fluids of the body is excellent.

Tends to be excreted slowly in the urine.

Toxicity:

Least of all the commonly used sulfanilamides which are absorbed from the bowel.

(Muether, R. O., *J. Missouri S. Med. Assn.*)

TABLE 16—SULFAGUANIDINE (SULFANYLGUANIDINE MONOHYDRATE)

Clinical Indications:

Disease: Bacillary dysentery and possible other bacillary infections of the gastrointestinal tract.

Possible Prophylaxis:

Preparation of the bowel for extensive surgery

Treatment of carriers of bacillary infections

Dose:

Initial Dose: 0.1 Gm. per kg. body weight.

Maintenance Dose: 0.05 Gm. per kg., divided into six doses and given every four hours until stools return to normal or the desired effect is obtained.

Absorption from the gastrointestinal tract is erratic but usually slight.

Diffusion into body fluids is as a rule poor

Excretion by kidneys not great.

Toxicity:

Toxicity is not great, although in some patients side effects are noted.

(Muether, R. O., *J. Missouri S. Med. Assn.*)

Sulfamerazine (Methylsulfadiazine): This recent addition to the sulfa family is said to have very low toxicity, to be quickly absorbed when taken by mouth, and to be less likely than any other sulfa drug to cause kidney damage. In comparison with sulfadiazine, it is said that when the two drugs are given in iden-

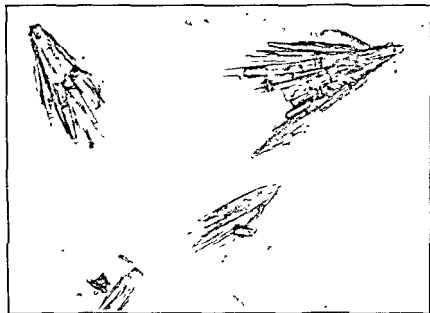


Fig. 2—Sulfapyridine crystals (magnified) washed from the urinary bladder.
(Plummer and McLellen / *A. M. A.*)

tical dosage by mouth, the sulfonamide concentration in the blood produced by the methyl compound is considerably greater. As the dosage of the two compounds is increased, this difference in the blood levels produced by equivalent doses becomes progressively more striking.

A given concentration in the blood, following oral administration of sulfamerazine, is not only produced by a smaller dose, but is also more rapidly attained than with sulfadiazine, due apparently to the more rapid and more complete absorption of the methyl compound. There has so far been insufficient clinical

experience with this drug to give data on its dosage in various diseases.

Murphy, Clark, and Flippin² gave a single dose of sulfamerizine to a group of persons orally, subcutaneously, intravenously,

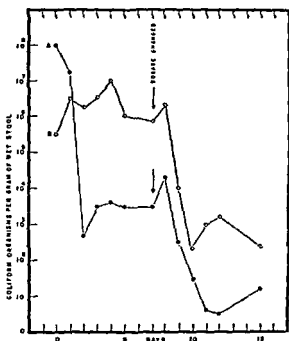


Chart 3—A demonstration of the apparently synergistic action of sulfathiazole and succinylsulfathiazole when simultaneously administered to the dog. A received daily 0.25 Gm. of succinylsulfathiazole per kg. in six doses for seven days. At this time a daily dose of 0.25 Gm. of sulfathiazole per kg. was added. B received 0.25 Gm. of sulfathiazole per kg. daily for seven days, then succinylsulfathiazole was added so that the animal thereafter took 0.25 Gm. per kg. of each drug daily.

(Poth, E. J., et al. *Arch Surg*)

or rectally, while multiple doses were administered over a period of days to another group. Their studies embraced 28 patients serving as controls and 20 patients with acute bacterial infection. The observations of these authors were that after a single 3-Gm. oral dose of sulfamerizine, higher blood serum levels are attained more rapidly and sustained longer than after similar amount of sulfadiazine. Desired serum concentrations can be

reached by giving sulfamerazine sodium subcutaneously or intravenously. The drug is readily diffused through body fluids and enters the red cells in varying concentrations. It is excreted in the urine in amounts roughly comparable to sulfadiazine.

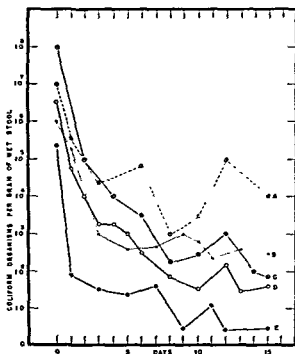


Chart 1—The effect of various dosages of succinylsulfathiazole on the coliform bacteria in the gastrointestinal tract of the dog. Each curve is based on the average effects observed in from three to five experiments. A represents the results after the oral administration of 0.05 Gm. per kg. daily, given in six equal doses at four-hour intervals; B, 0.1 Gm. per kg.; C, 0.25 Gm. per kg.; D, 0.5 Gm. per kg.; E, 1.0 Gm. per kg. (Poth, E.), et al. *Arch Surg.*)

Hall and Spink^{2a} used sulfamerazine in the treatment of 116 patients having a variety of infections, and compared it with sulfadiazine with respect to its pharmacology, therapeutic effectiveness, and toxicity. Adequate blood concentrations, they say, can be maintained with smaller doses of sulfamerazine than with sulfadiazine. Because sulfamerazine is retained in the body for a longer period of time than sulfadiazine, doses of the former may be given at less frequent intervals. Sulfamerazine appears to be

just as effective in the therapy of pneumococcic pneumonia as sulfadiazine. Sulfamerazine usually caused a more abrupt fall in temperature than occurred with sulfadiazine. Sulfamerazine also appeared to be just as effective as sulfadiazine or sulfapyridine in the treatment of meningitis due to type B influenza bacillus or the meningococcus. Infections due to hemolytic

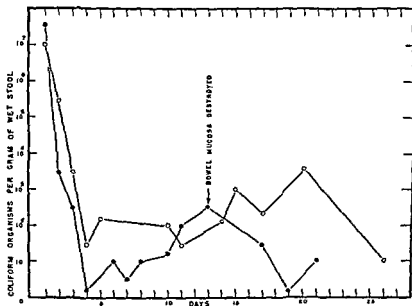


Chart 2—To demonstrate the effect of lesions of the mucous membrane on the antibacterial activity of succinylsulfathiazole, the number of coliform organisms was reduced by the administration of the drug. Then the mucosa of a large area of the descending colon of the dog was destroyed by cauterization.

(Poth, E. J., et al., *Arch. Surg.*)

streptococci responded quite satisfactorily to sulfamerazine, and in this respect the results were similar to those obtained with sulfadiazine. Sulfathiazole is more effective than either sulfamerazine or sulfadiazine in staphylococcic infections. Toxic reactions due to sulfamerazine were no more frequently encountered than with sulfadiazine. Sulfamerazine provoked fewer reactions than we had previously encountered with sulfathiazole, sulfapyridine or sulfanilamide. Although sulfamerazine and its acetyl-

ated form are more soluble in urine than the comparable forms of sulfadiazine, two of the patients developed renal complications due to precipitation of the drug in the form of crystals within the urinary tract.

Recent investigations would indicate that crystalluria due to sulfadiazine may be prevented, or at least reduced, by administering sufficient quantities of an alkali so that the pH of the urine is maintained at 7.5 or higher. To achieve such an alkaline urine when therapeutic doses of sulfadiazine are being utilized, it has been recommended that from 10 to 20 Gm. of sodium bicarbonate should be administered in divided doses every 24 hours. As a result of a group of preliminary observations, we are in agreement with the foregoing recommendation. It would also appear that alkalization is a valuable prophylactic procedure for patients receiving sulfamerazine. This is well illustrated in the following example:

A woman aged 33 at the University Hospitals had subacute bacterial endocarditis due to streptococci of the viridans group. Sulfonamide therapy had failed to clear the blood stream of bacteria. It was decided to give a large dose of sodium sulfamerazine in an attempt to control the infection. She was given 3 Gm. of sodium bicarbonate five times a day, and the 24-hour fluid intake was maintained around five liters. Twenty-five Gm. of sodium sulfamerazine were given intravenously. The 24-hour fluid intake on this day was 5300 cc. and the urinary output was 1700 cc. The following 24-hour intake of fluid was 4050 cc. with an output of 3505 cc. of urine. The maximum concentration of sulfamerazine in the blood was 68 mg. of the free drug. The hydrogen ion concentration of the urine was maintained above a pH of 8. At no time were sulfamerazine crystals observed microscopically in freshly voided specimens of urine. There was no evidence of gross or microscopic hematuria, and the patient had no symptoms referable to the urinary tract. She had several emeses, complained of a headache, and appeared mentally confused and depressed for a short time. The procedure failed to sterilize her blood.

On the basis of this and similar observations, we have recommended at the University Hospitals that in patients receiving sulfadiazine or sulfamerazine a fluid intake should be maintained so that the urinary output during a period of 24 hours ranges between 1000 and 2000 cc. At the same time, enough sodium bicarbonate should be administered so that the pH of the urine is 7.5 or more. Obviously, such a procedure is carried out in patients whose clinical condition does not contraindicate these procedures. This applies particularly to patients having renal dysfunction or cardiac failure. It should be emphasized that renal complications due to sulfapyridine, sulfathiazole, sulfadiazine, and probably sulfamerazine may be due to factors other than the precipitation of crystals. There is considerable evidence that renal failure may be associated with a direct toxic effect of the sulfonamides on the renal parenchyma and also due to hypersensitivity phenomena. It is doubtful that alkalization would be of much benefit under such circumstances.

Sulfamerazine appears to be tolerated quite well by children and small infants. No toxic reactions were encountered in 15 infants under one year of age.

Succinylsulfathiazole (Sulfasuxidine): Succinylsulfathiazole, say Poth and Knotts,³ is so poorly absorbed from the gastrointestinal tract that only an average of five per cent of the ingested drug is excreted by the kidneys. Its action after oral administration, therefore, is essentially restricted locally to the contents of the bowel. The feces, which contain a moderate amount of mucus, become small in bulk, semifluid, and relatively odorless. Ordinarily there will be two to four stools daily without hyperperistalsis or griping pain. Rarely does true diarrhea occur. The bacterial flora are profoundly altered; this is indicated by the effect on the coliform organisms. While the change in the coliform flora is used as an indicator of drug effect, it must be realized that all organisms in the bowel more susceptible than *Bacillus coli* to the antibacterial action of succinylsulfathiazole are even more profoundly affected. The Shiga, Flexner, and Sonne strains of the dysentery bacillus are espe-

cially susceptible to the antibacterial action of this compound. The drug has no apparent effect on the growth of the typhoid and paratyphoid organisms, alpha *Streptococcus fecalis*, or *Bacillus proteus*. *Bacillus aerobacter aerogens* is more resistant than *B. coli* to the action of succinylsulfathiazole. The change in the character of the stools, including the disappearance of the fecal odor, suggests strongly that the growth of anaerobic proteolytic bacteria is particularly inhibited.

Accurate knowledge of the mode of action of sulfanilamide and its derivatives is as yet lacking. Theoretically, paraämino-benzoic acid or some chemically similar compound combines with a hypothetic substance, possibly an enzyme, to form a metabolite essential to the normal growth processes of certain bacteria. For the sake of simplicity we shall refer to this hypothetic substance as X. It is not known whether X is an endogenous or an exogenous substance as regards the bacterial cells. Fleming showed that dead bacteria added to media interfered with the action of sulfanilamide. It is not inconceivable that X may be formed principally by certain strains of bacteria and that it may even be a factor in the phenomenon of symbiosis.

TABLE 17—PATIENTS GROUPED ACCORDING TO CONDITION

<i>Group</i>	<i>Condition</i>	<i>Patients</i>
1	Convalescent, with normal intact intestinal mucosa	5
2	Typhoid fever	12
3	Bacillary dysentery	19
4	Diarrhea (nonspecific)	14
5	Carcinoma of the right colon	4
6	Carcinoma of the left colon	15
7	Carcinoma of the transverse colon	2
8	Fecal fistulas involving the colon	3
9	Fecal fistulas involving the small bowel	3
10	Chronic ulcerative colitis	10
11	Diverticulitis	3
Total ..		100

(Pooh, E. J., and Knotts, F. L. *Arch. Surg.*)

The present concept of the mechanism and the competitive nature of the reactions of sulfanilamide and its derivatives and paraaminobenzoic acid is that the former act because of their tendency to combine with substance X to form a conjugated compound unsuited to the metabolism of bacteria. From this concept it becomes obvious that X is rendered suitable for further metabolic processes, depending on whether it is coupled with sulfanilamide or one of its derivatives as expressed by equation 1 or with paraaminobenzoic acid as indicated in equation 2.

Sulfanilamide or one of its derivatives + substance X \rightarrow Inactive substance (1).

Paraaminobenzoic acid + substance X \rightarrow Metabolic enzyme or metabolite (2).

Because of the small bulk and the semifluid character of the feces, the contents of the bowel come into frequent and close contact with the absorbing mucosa. Since it is likely that paraaminobenzoic acid, similar split products, and substance X are readily absorbed from the bowel, it can be assumed that the concentrations of these substances, which would favor the formation of the metabolic enzyme, will tend to be lowered and that thus the interaction of sulfanilamide or one of its derivatives and substance X to form a compound unsuitable for enzymatic utilization by the bacteria will be unopposed.

Further understanding of the mode of action of succinylsulfathiazole in the bowel might be forthcoming from an examination of certain conditions unfavorable to the action of the drug.

The following facts have been observed:

1. Liquid petrolatum interferes with the antibacterial activity of succinylsulfathiazole.
2. Watery diarrhea due to irritation of the mucosa strongly inhibits the antibacterial action of the drug.
3. Hard, constipated stools, which do not become semifluid after the administration of succinylsulfathiazole, show only a partial lowering of the number of susceptible organisms.

TABLE 18—HYDROLYSIS OF SUCCINYLSULFATHIAZOLE IN FECES AND IN THE AQUEOUS SOLUTION OF THE SODIUM SALT*

Days in Incubator at 37° C	Molecular Concentration and Ratio of Sulfathiazole and Succinylsulfathiazole					
	In Incubated Stool Specimen			In Incubated Solution of Sodium Salt of Succinylsulfathiazole		
	Free (mM per L.)	Conjugated (mM per L.)	Ratio Conjugated-Free	Free (mM per L.)	Conjugated (mM per L.)	Ratio Conjugated-Free
0	2.55	65.2	25.6	34.6	550	15.9
4	8.05	59.1	7.4	30.7	510	16.6
13	9.8	54.9	5.6	34.8	635	18.2
34	13.3	40.4	3.0	40.35	624	15.2
41	61.5	40.0	2.4	46.4	660	14.2
48	16.85	50.0	2.9	39.6	663	16.7
63	16.5	55.0	3.3	34.4	507	14.7

*Within the rather wide limits of the accuracy of the analytic procedure a freshly expelled stool specimen contains only relatively small quantities of sulfathiazole. At 37° C. succinylsulfathiazole in contact with fecal material undergoes hydrolysis. This may be due to action of bacteria or ferments. The aqueous solution of succinylsulfathiazole sodium is relatively stable. (Poth, E. J., et al. *Arch Surg*)

4. On incubation at 37° C., the coliform organisms may multiply rapidly in some specimens of feces intimately mixed with succinylsulfathiazole.

5. The presence of extensive ulcerative lesions of the intestinal tract retards the rate at which the coliform organisms disappear under therapy, and the final level of the coliform population probably remains somewhat higher than in those instances in which the mucosa of the bowel is intact.

It has been observed that freshly voided feces contain only relatively small amounts of sulfathiazole, but that after they stand at 37° C. the succinylsulfathiazole is slowly and progressively hydrolyzed to give free sulfathiazole (Table 17). Although the amount of free sulfathiazole present in freshly voided feces is small as compared to the amount of succinylsulfathiazole, the concentration of the free sulfathiazole may vary ordinarily from 50 to 200 mg. per 100 cc. Such concentrations of sulfathiazole

should be sufficient to have strong bacteriostatic activity without any special assumptions as to the excited state of the sulfathiazole molecule.

Phthalylsulfathiazole: Endeavoring to find a perfect intestinal antiseptic Poth and Ross,⁴ in a manuscript not yet published, describe phthalylsulfathiazole. The drug is practically insoluble in water and is a weak acid. The finely divided

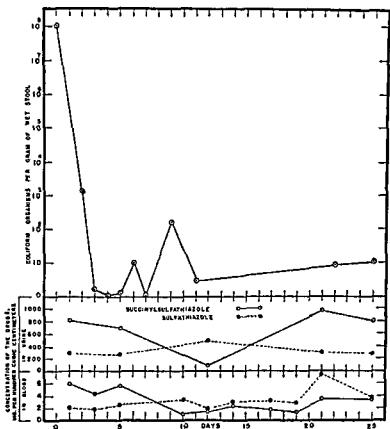


Chart 4—The significant lowering of the number of coliform bacteria in the bowel of the dog after the daily oral administration of 1 Gm. per kg. of succinylsulfathiazole divided into six equal doses. The concentrations of the drug in the blood and the urine are given. The degree to which hydrolysis of succinylsulfathiazole is effected to yield sulfathiazole is indicated by the concentration of the latter in the blood and the urine.

(Poth E J., et al. *Arch Surg*)

powder suspended in an aqueous sodium bicarbonate solution will liberate carbon dioxide slowly at room temperature. The sodium salt is moderately soluble. A 20 per cent aqueous solution of the salt can be prepared if a ten per cent excess of sodium hydroxide is used. The sodium salt can be recovered from this solution by chilling in an ice bath, and it can be further purified by recrystallization from water buffered to pH 7. Care should be taken not to warm the solution above 50° C., because of the tendency of this compound to hydrolyze.

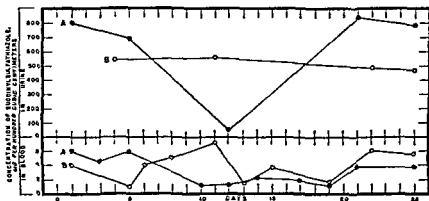


Chart 5—Illustration of the fact that an animal (A) receiving daily 1 Gm. of succinylsulfathiazole per kg. divided into six equal oral doses has essentially the same concentration of the drug in its blood and urine as another animal (B) similarly receiving a dosage of 0.25 Gm. per kg.

(Poth, E J, et al Arch Surg)

Phthalylsulfathiazole, say the authors, has from two to four times greater bacteriostatic activity than succinylsulfathiazole, as indicated by the effect on coliform organisms in the gastrointestinal tract of the dog. A dose as small as 0.125 Gm. per kg. of body weight per day causes a significant lowering in the coliform population. Doses of 0.25 Gm. or more per kg. of body weight, administered at regular four hourly intervals to animals on a straight meat diet, causes more profound and more rapid alterations in the bacterial counts. With doses of 0.25 Gm. per kg. or more, frequently no coliform organisms grow out after the third day of administration. It has been

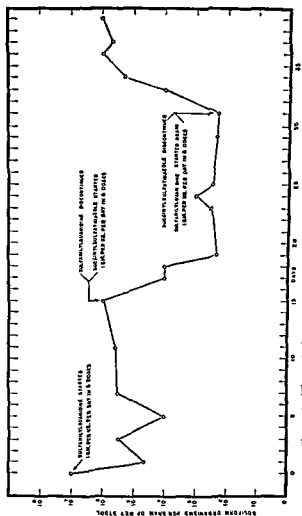


Chart 6.—The relative antibacterial activity of sulfanilylguanidine and succinylsulfathiazole as demonstrated by the effects of these drugs on the coliform organisms in the bowel of the dog. (Petb, E. J. *et al.* *Arch. Surg.*)

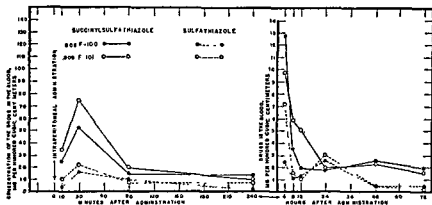


Chart 7—Illustration of the rapid rate of absorption after the intraperitoneal injection of an aqueous suspension of 1 Gm. per kg. of succinylsulfathiazole and the rate of its disappearance from the blood.

(Poth, E. J., et al.: *Arch. Surg.*)

noticed also that when phthalylsulfathiazole is administered by other than the oral route so as to maintain a high tissue concentration, that the drug is excreted into the bowel to give concentrations of the drug in the feces which result in inhibition of the coliform organisms. This alteration is somewhat more delayed than when the drug is administered by mouth, although it may frequently be of the same order of magnitude. Animals have been fed the drug for as long as 35 days, during

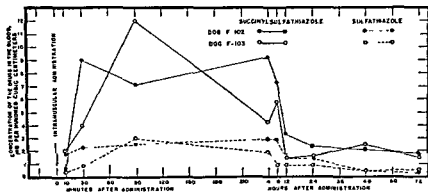


Chart 8—The concentration of sulfathiazole and succinylsulfathiazole in the blood after the intramuscular administration of an aqueous suspension of 1 Gm. per kg. of succinylsulfathiazole.

(Poth, E. J., et al.: *Arch. Surg.*)

which time the marked suppression of the coliform flora has been maintained.

Phthalylsulfathiazole and its sodium salts are so sparingly absorbed from the gastrointestinal tract that, regardless of the dose, no toxicity can be demonstrated. Dogs have been maintained on an oral dose of phthalylsulfathiazole of 0.5 Gm. per kg. of body weight per day, divided into six equal portions and administered at four-hour intervals for periods as long as six weeks, without the development of evidence of toxicity.

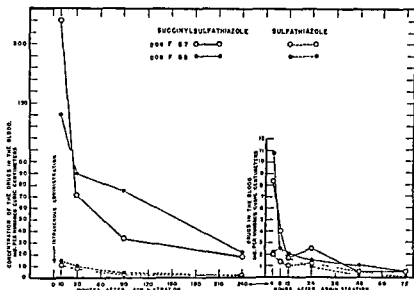


Chart 9—The rapidity with which the drug disappears from the blood after the intravenous injection of 1 Gm. per kg. of the sodium salt of succinyl-sulfathiazole.
(Puth, E. J., et al. *Arch Surg.*)

Hypodermoclysis: When patients cannot take the sulfonamides orally for any reason, the sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine may be conveniently and safely administered subcutaneously. This method of administration has been reported by Taplin, Custer, and Young.⁵

The majority of the patients of these authors were treated with 0.5 per cent sodium sulfonamide solutions, made by dis-

solving 5 Gm. of the sodium sulfonamide in one liter of isotonic solution of three chlorides, isotonic solution of sodium chloride, or one-sixth molar sodium lactate solution. Concentrations of the sulfonamide compounds as high as 0.8 per cent were used. Isotonic solution of sodium chloride was the vehicle most commonly employed.

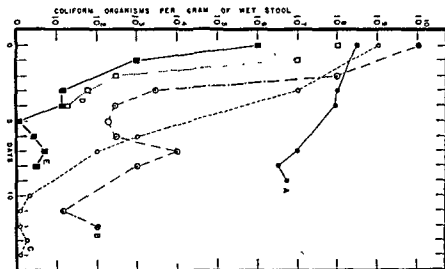


Chart 10—The effect of varying dosages of succinylsulfathiazole on the coliform bacteria in the gastrointestinal tract of man: *A* diagrams the results of the oral administration of 0.1 Gm. per kg. divided into six equal doses. *B* represents the effect of the similar administration of 0.2 Gm. per kg.; *C*, the effect of 0.25 Gm. per kg.; *D*, the effect of an initial dose of 0.25 Gm. per kg. followed after four hours by 0.25 Gm. per kg. per day in six equally divided doses (this patient had large ulcerating carcinoma of the rectum); *E* represents the course after the oral administration of three massive doses of 0.25 Gm. per kg. at four-hour intervals followed by 0.25 Gm. per kg. per day divided into six equal quantities. (Poth, T. J., et al. *Arch. Surg.*)

The solutions were prepared in one of the following ways: (1) The sodium sulfonamide was added to the vehicle and the mixture heated to the boiling point and allowed to cool to body temperature before administration. (2) The vehicle was first heated to the boiling point and allowed to cool slightly and then the drug was added. After cooling the solution was ready for

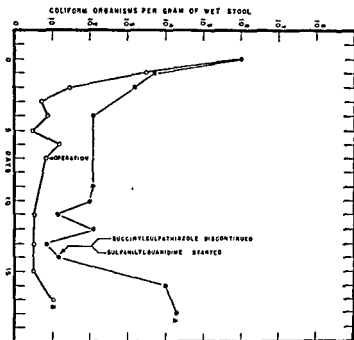


Chart 11—The relative antibacterial activity of succinylsulfathiazole and sulfanilylguanidine as demonstrated by the effects of these drugs on the coliform organisms in the bowel of man after oral administration. A received 0.25 Gm. of succinylsulfathiazole per kg. daily in three equal doses for 14 days. This dosage was discontinued, and the maximum recommended dosage of sulfanilylguanidine, 2 Gm. every four hours, was started immediately. B, after receiving 10.5 Gm. of sulfanilylguanidine daily for 14 days, had 1,000,000 *B. coli* per Gm. of wet stool as indicated on day 0 of the chart. The curve indicates the course after the daily oral administration of 0.33 Gm. per kg. of succinylsulfathiazole: A had an intact normal gastrointestinal tract; B was suffering from chronic ulcerative colitis.

(Poth, E. J., et al. *Arch. Surg.*)

use. The first method is the more convenient, but either may be used without apparent difference in blood concentration or therapeutic response.

The pH values of the sulfonamides in saline solution, as determined by the Beckman apparatus, were as follows: Sodium sulfapyridine, 10.0; sodium sulfathiazole, 9.5, and sodium sulfadiazine, 9.2. In spite of the decided alkalinity, these solutions caused no local reactions when injected under the skin.

TABLE 19—DOSAGE OF SUCCINYLSULFATHIAZOLE

Concentration of the Drug in the Blood and the Feces and the Quantity of the Drug Excreted in the Urine in Cases in Which the Gastro-intestinal Tract Exhibited Various Lesions

Patient and Weight, kg	Day	Daily Dose, Gm., Divided Into Six Equal Doses	Concentration of the Drug in the Blood, mg per 100 cc		Daily Urinary Output, Gm		Concentration of the Drug in the Stools, per Cent	Comments
			Free	Conjugated	Free	Conjugated		
M. N. 56	1	28			0.07	0.07		Large ulcerating carcinoma of rectum. B. coli count dropped from 10^8 to 10^3 operation done after only three days of treatment with drug. postoperative course uneventful, no distention, nausea or vomiting, no toxic symptoms, 8.2 per cent of ingested drug excreted in urine
	2	28	1.3	5.6	0.34	0.40	7.5	
	3	14	0.8	1.2	0.33	0.58	05.1	
	4		0.84	1.0				
	5	14	1.17	1.2	0.50	0.49		
	6	14	1.30	1.0	0.47	0.76		
	7	14	1.30	1.0	0.37	0.82		
	8	9	1.30	1.2	0.41	0.97	8.0	
	9				0.22	0.62	6.0	
	10				0.13	0.45		
	11				0.06	0.15		
	12				0.06	0.18		
P. R. 70	1	24			0.24	0.25		Ulcerating carcinoma of rectum, coliform organisms dropped from 10^8 to 10^3 in four days and remained at this level, operation on ninth day, no postoperative complications, no distention, no gas pains after abdominal perineal resection, no toxic manifestations, 6.85 per cent of ingested drug excreted in urine
	2	18	1.08	2.50	0.47	1.57		
	3	18	1.50	4.70	0.30	0.70		
	4	18	0.80	0.80	0.23	0.46	5.7	
	5	18	1.30	0.20	0.24	0.42	4.8	
	6	18	0.80	3.4	0.54	1.00	4.6	
	7	18	1.00	3.00	0.20	0.40	4.9	
	8	18	1.30	0.80	0.35	0.35	10.5	
	9	12	1.30	2.30	0.04	0.04		
	10	6	1.20	0.00	0.35	0.22		
	11	18	0.80	1.20	0.78	0.34		
	12	6	0.80	2.80	0.60	0.02	3.5	
	13		0.75	0.10	0.50	0.57	4.5	
	14		1.00	0.33	0.02	0.00		
	15		1.2	0.60	0.03	0.00		
	16		0.20	0.00	0.00	0.00		
M. E. 75	1	25						Partial obstruction in sigmoid on basis of old diverticulitis, drug given five days before operation, bowel wall much thickened and scarred with numerous small sinuses and diverticula, few small sessile polyps present, some soiling at time of operation, postoperative course uncomplicated—no distention or gas pains, B. coli count dropped from 10^8 to 60 organisms per Gm. of wet stool, although previously there had been a drug reaction with a rash after sulfathiazole therapy, there were no toxic manifestations due to administration of succinylsulfathiazole, 5.8 per cent of ingested drug excreted in urine
	2	18	1.0	1.5	0.28	1.0		
	3	18	0.8	1.4	0.14	1.24		
	4	18	0.5	1.4	0.70	0.28	6.9	
	5	15	1.8		0.67	0.00		
	6	0	1.2	3.3	0.21	0.23	8.0	
	7	15			0.13	0.02		
	8	18	1.0	1.2	0.47	0.82		
	9	18	1.2	1.6	0.24	0.15		
	10	18	0.8	1.7	0.46	1.18		
	11	18	1.3	1.8	0.34	0.21		
	12	18			0.27	0.27		
	13	18	1.3	2.5	0.43	0.66	5.7	
	14	18			0.26	0.50		
	15	18	0.7	2.2	0.27	0.61		
	16	18			0.60	1.33	5.2	
	17				0.26	0.64		
	18	..	0.8	1.7	0.10	0.26	4.4	
	19				0.10	0.23	1.2	
	20	..	0.1	0.4	0	0.10		

TABLE 19—Continued

Patient and Weight, kg	Day	Daily Dose, Gm., Divided Into Six Equal Doses	Concentration of the Drug in the Blood, mg. per 100 cc		Daily Urinary Output, Gm		Concentration of the Drug in the Stool*, per Cent	Comment
			Free	Conjugated	Free	Conjugated		
B. D. 55	1	30						Operation several months previously for abscess resulting from perforation of descending colon by fish bone, fecal fistula resulted, actinomycosis found on one examination, attempt made to close fistula without success, sulfathiazole therapy did not prevent extensive breakdown of wound resulting in formation of double barreled colostomy, three months later succinylsulfathiazole given (0.25 Gm. per kg by mouth and 0.25 Gm. per kg in distal limb of colostomy daily), because of involvement of soft tissues sulfathiazole was given beginning on ninth day to saturate general body tissues, colostomy closed on thirteenth day, sulfathiazole discontinued on twenty-sixth day, after operation 0.25 Gm per kg daily of succinylsulfathiazole given by mouth, postoperative course uneventful, no toxic manifestations, coliform count dropped from 10 ⁸ to 0
	2	27	0.6	1.4	0.19	0.36	4.2	
	3	27	0.7	1.5	0.14	0.22	6.5	
	4	27			0.27	0.28	8.1	
	5	27	1.3	1.6	0.09	0.20		
	6	27	0.8	1.4	0.10	0.22		
	7	27	0.4	1.0	0.28	0.28	8.3	
	8	27	0.3	2.2	0.40	0.01	6.6	
	9	27	1.8	2.1	0.16	0.10	4.2	
	10	27	1.4				5.5	
	11	27						
	12	22.5	5.3	0.8			1.6	
	13	0	2.4	4.4			4.9	
	14	11						
	15	13.5	7.2	1.2				
	16	13.5					1.4	
	17	13.5	5.4	2.4			3.4	
	18	13.5						
	19	13.5	4.0				4.8	
	20	13.5					5.4	
	21	13.5					5.3	
	22	13.5	4.4	1.7				
	23	13.5						
	24	13.5	4.9	0.8				
	25	13.5						
	26	13.5	5.9	0.4				
	27	13.5						
	28	13.5	0.9	1.0				
	29	13.5						
	30	13.5						
	31	13.5						
L. N. 27	1	13.7	0.9	1.5	0.28	0.30		Boy ten years old with kidney stone, ileostomy and extensive prolapse of ileostomy, operative treatment shown in fig. 1D, coliform organisms dropped from 10 ¹⁰ to less than 10, uneventful postoperative course, no toxic drug reaction, six per cent of ingested drug excreted in urine
	2	7.5			0.07	0.01		
	3	7.5	0.7	0.8	0.22	0.03		
	4	7.5			0.20	0.42		
	5	7.5			0.17	0.02		
	6	7.5			0.37	0.61		
	7	7.5	1.7	1.0	0.31	0.86		
	8	7.5			0.27	0.58		
	9	7.5	1.6	1.6	0.10	0.12		
	10	7.5			0.08	0.25		
	11	7.5	1.4	3.0	0.08	0.26		
	12*				0.09	0.17		
	13	7.5			0.08	0.14		
	14	7.5			0.21	0.28		
	15	7.5			0.34	0.93		
	16	7.5			0.17	0.31		
	17	7.5	0.9	2.5	0.17	0.41		
	18	7.5			0.18	0.43		
	19	7.5			0.16	0.19		
	20	7.5			0.06	0.04		
	21	7.5			0.11	0.09		
	22	13	0.4	0.2	0.22	0.22		

* Day of operation.

TABLE 19—Continued

Patient and Weight, kg	Day	Daily Dose, Gm., Divided Into Six Equal Doses	Concentration of the Drug in the Blood, mcg. per 100 cc		Daily Urinary Output, Gm		Concentration of the Drug in the Stool, per Cent	Comment
			Free	Conjugated	Free	Conjugated		
T S 52	1	21	14	12	0.01	0.24		Woman 49 years old with rectal bleeding for two months, polypoid adenocarcinoma of sigmoid, coliform count dropped from 10 ⁷ to less than 10, open resection of sigmoid with end to end suture, postoperative course uneventful as regards gastrointestinal tract, sustained radial palsy during operation, after operation sulfathiazole given for pulmonary complication, drug reaction with kidney damage, prior to sulfathiazole therapy 38 per cent of ingested succinylsulfathiazole excreted in urine, high blood levels from nineteenth day due to administration of sulfathiazole
	2	13	04	19	0.17	0.16		
	3	12			0.31	0.51		
	4	12	10	14	0.20	0.23		
	5	12			0.15	0.30		
	6	12	11	16	0.14	0.16		
	7	12	07	0	0.15	0.20		
	8	12			0.19	0.21		
	9	12			0.19	0.11		
	10	12			0.16	0.05		
	11	8	09	03	0.17	0		
	12	12	04	16	0.52	0.50		
	13	12	05	13	0.18	0.23		
	14	12			0.16	0.03		
	15	12			0.24	0.24		
	16	12			0.15	0.30		
	17	12			0.05	0.07		
	18*							
	19		35	53	1.06	0.45		
	20	12	83	25	3.95	2.41		
	21	12			2.90	1.40		
	22	12	58	36				
	23	12						
	24	12			2.66	2.05		
	25	12			1.47	0.93		
	26	12			1.86	2.07		
	27	12						
	28	12						
	29	12			1.06	1.64		
	30	6	68	1.6	0.74	0.38		
E. A 72	1	33						Filipino man 43 years old with long history of pain in right lower quadrant of abdomen, exacerbation for past three weeks with palpable mass in right lower quadrant of abdomen, operation delayed because of question regarding diagnosis, tumor of cecum found at operation, resection of colon on right side to midtransverse with open ileocolostomy, postoperative course uneventful, dismissed on seventeenth postoperative day, coliform count dropped to 600, no toxic drug reactions, 41 per cent of ingested drug excreted in urine
	2	18						
	3	18						
	4	18	0.86	2.64				
	5	18						
	6	18						
	7	18						
	8	18	0.86	2.83				
	9	18						
	10*				2.19†	1.78†		
	11	5			0.055	0.058		
	12	15			0.059	0.043		
	13	15.5			0.60	0.445		
	14	18	1.29	0.18	0.94	0.62		
	15	18			0.236	0.416		
	16	18			0.14	0.23		
	17	18			0.29	0.40		
	18	18			0.33	0.35		
	19	18			0.29	0.42		
	20	18			0.22	0.35		
	21	18	0.32	2.06	0.27	0.33		
	22	18			0.29	0.37		

* Day of operation

TABLE 19—Continued

Patient and Height, kg	Day	Daily Dose, Gm; Divided Into Six Equal Doses	Concentration of the Drug in the Blood, mg. per 100 cc		Daily Urinary Output, Gm		Concentration of the Drug in the Stools, per Cent	Comment
			Free	Conjugated	Free	Conjugated		
L. E. 49	1	24						Woman 57 years old with focal fistula after resection of cecum for carcinoma six years before present admission, coliform count dropped from 10 ⁸ to less than 10, operative procedure shown in fig 1C, superficial wound infection and alpha Str faecalis cystitis after operation, postoperative course otherwise uneventful, dismissed on 22d day after operation, no toxic reaction to drug, 6.4 per cent of ingested drug excreted in urine
	2	12	0.86	8.12				
	3	12						
	4	12						
	5	12						
	6	12						
	7	12						
	8	12						
	9	12						
	10	12						
	11	12						
	12*				2.54†	7.15†		
	13	6			0.16	0.033		
	14	12	1.73	0.72				
	15	12						
	16	12						
	17	12						
	18	12			0.251	0.366		
	19	12			0.094	0.122		
	20	12			0.062	0.076		
	21	12						
	22	12	0.43	1.55	0.128	0.156		
	23	12						
	24				0.064	0.142		
H. S. 45.4	1	4						Negro woman 63 years old with severe diarrhea and large amounts of blood in stools, hemoglobin content, twenty per cent, carcinoma of hepatic flexure, repeated transfusions, coliform count did not drop until diarrhea was controlled with lead and opium, count then dropped immediately from 10 ⁸ to 700, resection of colon on right side with ileotransversostomy, postoperative course uncomplicated, no toxic drug reaction, dismissed on 20th post-operative day, 2.4 per cent of ingested drug excreted in urine, hemoglobin content, 80 per cent.
	2	12			0.000	0.025		
	3	12			0.128	0.354		
	4	12			0.010	0.023		
	5	12			0.113	0.272		
	6	12			0.062	0.176		
	7	12						
	8	15	0.86	2.68	0.035	0.094		
	9	18			0.092	0.193		
	10	18			0.036	0.082		
	11	18						
	12	18						
	13	18						
	14	18						
	15	18			0.039	0.145		
	16	12						
	17*				0.115	0.326		
	18	12						
	19	18			0.101	0.224		
	20	18						
	21	18			0.118	0.171		
	22	18			0.047	0.146		
	23	18			0.036	0.046		
	24	18			0.035	0.059		
	25	18			0.083	0.089		
	26	18			0.197	0.302		
	27				0.065	0.119		
	28				0.294	0.336		

* Day of operation

TABLE 19—Continued

Patient and Weight, kg	Day	Daily Dose, Gm; Divided Into Six Equal Doses	Concentration of the Drug in the Blood, mg. per 100 cc		Daily Urinary Output, Gm		Concentration of the Drug in the Stools, per Cent	Comment
			Free	Conjugated	Free	Conjugated		
G R.	1	15			0.103	0.231		Woman 33 years old with multiple fecal fistulas, five previous abdominal operations, including colectomy and ileosigmoidostomy, coliform organisms dropped from 10 ⁷ to 10 ³ , extensive operation with open end to side anastomosis of bowel in presence of a massive adhesion, course uncomplicated, all fistulas closed, no toxic drug reaction, 3.7 per cent of ingested drug excreted in urine, dismissed on 22d postoperative day
	2	15			0.255	0.796		
	3	15	0.43	1.42	0.158	0.536		
	4	15			0.104	0.294		
	5	15			0.309	0.556		
	6	15			0.202	0.493		
	7	15						
	8	19	1.08	0.86	0.176	0.300		
	9	27			0.316	0.845		
	10	27			0.257	0.655		
	11	27	1.08	2.12	0.306	0.977		
	12	27			0.212	0.590		
	13	27			0.202	0.501		
	14	27			0.426	0.644		
	15	27			0.145	0.614		
	16*	15			0.234	0.938		
	17	5			0.072	0.223		
	18	15			0.044	0.108		
	19	15			0.310	0.325		
	20	15			0.172	0.185		
	21	15			0.172	1.242		
	22	15	1.38	2.84	0.530	0.596		
	23	15			0.128	0.255		
	24	15			0.119	0.180		
	25	15			0.127	0.133		
	26	15			0.026	0.026		
	27	15			0.094	0.023		
	28	15			0.050	0.113		
	29				0.062	0.041		
	30				0.034	0.082		
	31				0.009	0.026		
	32				0.024	0.000		
	33		0.43	0.74				
	34				0.004	0.000		

* Day of operation.

† Total preoperative urinary excretion

* Day of operation

† Total preoperative urinary excretion

(Poth, E. J., et al. *Arch. Surg.*)

The solutions described were injected into both thighs by hypodermoclysis over periods of from two to five hours. Some patients were given an initial intravenous injection of from one-fifth to one-third of the prepared 0.4 per cent to 0.8 per cent sulfonamide solution over a 20- to 30-minute period. The remaining portion of the solution was then given by hypodermoclysis.

From 19 patients blood samples for sulfonamide determinations were taken, in most instances at the following intervals

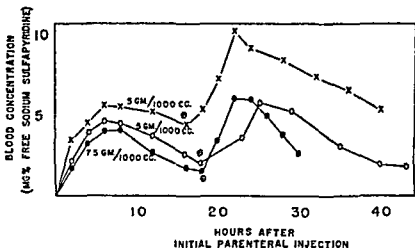


Chart 12—The blood concentration curves following the parenteral administration of sodium sulfapyridine to three patients. The two patients whose curves are indicated by solid dots and hollow dots received an initial hypodermoclysis of 7.5 Gm. and 5 Gm. respectively of sodium sulfapyridine in 1000 cc. of saline solution. The patient whose curve is indicated by X's received an initial intravenous injection of 2 Gm. of sodium sulfapyridine in 400 cc. of saline solution. Immediately thereafter a hypodermoclysis of 3 Gm. of sodium sulfapyridine in 600 cc. of saline solution was administered. At the points indicated by a circled plus sign a second hypodermoclysis of 1000 cc. was given to each patient. The concentration of the second clysis was the same as that previously given.

(Taplin, G. V., et al.: J. A. M. A.)

after treatment was started: 2, 4, 6, 8, 10, 12, 20, and 24 hours. In some instances, when indicated, a second or even a third hypodermoclysis was given. As a rule, it was possible to give the drugs orally after the patient had received from 5 to 20 Gm. of the sulfonamide compound subcutaneously. The trend of blood concentrations after hypodermic administration of three sulfonamide compounds is illustrated in Charts 12, 13, and 14.

In a personal communication Dr. Young states: "We no longer boil our solutions, but use sterile sodium salts instead, and we now use smaller doses at more frequent intervals. We have yet to experience any unfavorable local reactions from the subcutaneous administration of the sodium salts. We are using sodium sulfadiazine almost exclusively, because the blood levels are, of course, much better maintained than with sodium sulfathiazole."

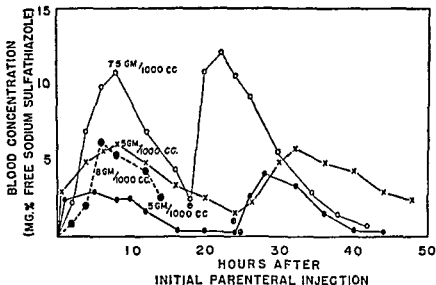


Chart 13—The blood concentration curves after parenteral administration of sodium sulfathiazole to four patients. The two patients whose curves are indicated by X's and small solid dots received an initial intravenous dose of 1 Gm. of sodium sulfathiazole in 200 cc. of saline solution. This was followed immediately by a hypodermoclysis of 800 cc. of the same 0.5 per cent solution. The two patients whose curves by hollow dots and large solid dots received hypodermoclysis initially of 1000 cc. of 0.75 per cent and 0.8 per cent sodium sulfathiazole in saline solution respectively. At the points indicated by a circled plus sign three patients received second hypodermoclyses of 1000 cc. Each of the latter doses corresponded in strength to that previously administered to each patient.

(Taplin, G. V., et al. • J. A. M. A.)

Sulfonamide Fastness⁶

The indiscriminate application of the sulfonamides to disease has emphasized the fact that they are not panaceas. Failures have occurred under conditions where sulfonamide therapeutic effectiveness has long been established.

Such circumstances occurring in sufficiently increasing frequency have chilled the enthusiasm of some investigators, causing them to lose interest in the sulfonamides generally and inviting them to turn their endeavors toward other possibilities such as gramicidin, penicillin, propamidine, acridine, and the like.

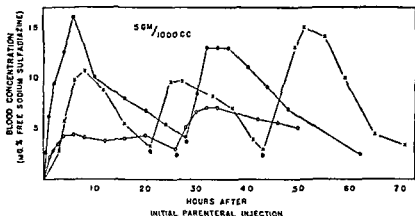


Chart 14—The blood concentration curves after the parenteral administration of sodium sulfadiazine to three patients. Each of these patients received an initial intravenous dose of 200 cc. of 0.5 per cent sodium sulfadiazine in saline solution, after which 800 cc. of the same solution was given as a hypodermoclysis. At the points indicated by a circled plus sign each patient received a second hypodermoclysis of 1000 cc. of the 0.5 per cent sodium sulfadiazine solution. One patient received a third hypodermoclysis of the same strength and amount.
(Taplin, G. V., et al. *J. A. M. A.*)

Earlier workers on the sulfonamides were impressed by the fact that certain substances inhibited the bacteriostatic activity when the drug was applied topically.

Decomposition of injured, nonviable tissues, degenerating cell bodies of the bacteria themselves, have long been known to destroy the chemotherapeutic effect of the drug. Methionine, paraaminobenzoic acid, peptone, tissue extract, and purulent exudate soon were included in the list of inhibitors.

Failures in the oral administration projected into the problem the resistant character of the bacteria themselves and their uncanny neutralizing counterattack.

Attempted explanations of these facts introduced the terms "sulfonamide fastness," "sulfonamide resistant."

Whether the predominating factor in this fastness is a natural self-resistance or an acquired insensitivity of the organism to the drug is not definite.

However, while self-resistant strains were isolated from cultures obtained in the presulfonamide era, the available evidence

indicates the probability of strains previously sensitive acquiring a tolerance, following repeated exposure to subtherapeutic quantities of the drug in the patient's tissues.

Inadequate sulfonamide dosage therefore is known to produce an acquired clinical resistance to further adequate drug therapy.

On the other hand, it has been demonstrated that a resistant strain can be transmitted from one host to another, retaining its drug-fastness property. This seems particularly true in *neisserian* infections, a circumstance which emphasizes the necessity of adequate dosage, the elimination of haphazard tests of cure and of premature cessation of treatment of defaulters.

Topically the presence of paraaminobenzoic acid in a lesion acts as a growth stimulant for certain bacteria and exerts a pronounced antisulfonamide activity.

These facts suggest that the self-resistant property of bacteria might depend upon the formation of paraaminobenzoic acid, the removal of which will minimize the antisulfonamide effect, azochloramid and urea (carbamide), among other substances, having singular promise in this regard.

Whether the activity of these substances is an enhancement of the sulfonamide effect alone or a neutralization of the inhibitor mechanism, or both, is debatable.

Decidedly synergistic against certain organisms, urea-sulfonamide has the advantage of being relatively nontoxic. It is a strong peptonizing agent exerting solvent action on necrotic tissue, pus, and detritus, thus chemically débriding contaminated wounds and mechanically at least removing inhibitors. It loses bacteria, rapidly deodorizing foul-smelling wounds, and renders sulfonamides more soluble. It stimulates granulations, vascularization, and hyperemia. Uniformly effective, it permits many variations in its therapeutic application.

Topical Use

Sulfanilamide usually is the drug of choice for topical use because of its solubility. The sodium salts of sulfapyridine, sulfathiazole, and sulfadiazine also are soluble, but their alkalinity

is high and they are therefore apt to be quite irritating. As stated under the section of Dosage of Sulfanilamide, this drug is used locally in a dosage of 1 Gm. for each ten square inches of surface involved, but in closed cavities not more than 5 Gm. should be used. At no time should more than 15 Gm. be used locally, for the drug is absorbed rapidly and toxic reactions can readily develop.

Oil Suspensions

Angevine⁷ has reported on the absorption and excretion of sulfonamide compounds suspended in oil. The author used soybean, corn, sesame, peanut, cottonseed, and olive oil, hydrous wool fat, and yellow petrolatum. The oils were commercial preparations not further purified, and of them the largest volumes of drug could be added to and the smoothest suspensions obtained with soybean oil, corn oil, and sesame oil. For a few days there is a slight separation of oil and drug on standing. However, the suspensions of sulfanilamide, sulfapyridine, and sulfadiazine can be remixed readily with a glass rod. The suspension of sulfathiazole can be remixed also, but with more difficulty. Even when kept at room temperature for three months suspensions are still apparently satisfactory. The sulfonamides mentioned above can be suspended in oil in high concentrations. Only slight local reaction occurred when the oil suspension of sulfonamide was injected subcutaneously. In animals a single subcutaneous injection of sulfanilamide, sulfathiazole, or sulfadiazine suspended in oil was absorbed at a uniform rate and, depending upon the dose, produced a concentration of the drug in the blood for as long as eight days. Excretion of the drug in the urine continued for several days after it had disappeared from the blood. Suspensions of sulfanilamide or sulfathiazole in soybean oil were instilled into the infected sinusal tracts of five patients with osteomyelitis. The drug was found in the blood for six days and continued to be excreted in the urine for as long as 137 days. The sinuses of two of the patients healed completely and those of the others im-

proved. The author believes that this method of therapy deserves further trial in chronic osteomyelitis and in other types of infected wounds.

Hemostasis

In the local treatment of osteomyelitis with sulfamethylthiazole powder it was noticed, according to Cunningham,⁸ that in wounds in which ordinarily there would be considerable post-operative oozing with subsequent saturation of the dressings, the sulfonamide caused them to remain almost uniformly dry. This observation prompted the thought that the drug might possess hemostatic powers of some degree.

A short time later a patient was admitted to the hospital bleeding from the left tonsillar fossa six days after tonsillectomy. The bleeding was of a persistent, oozing type, and had failed to respond to the usual methods of control, such as sedation, cleaning of the fossa, local application of pressure, and the application of snake venom to the fossa. The bleeding arose in the lower pole of the tonsillar fossa, close to the base of the tongue. The fossa was wiped dry and a small amount of sulfamethylthiazole powder was applied lightly with a sponge. A thin yellow scum formed on the surface of the tissue and the oozing ceased almost immediately.

In laboratory experiments which followed, scabs were evulsed and the oozing wounds sprayed with the various powdered drugs, a powder blower being used. Wounds were sprayed with powder until they were thoroughly and smoothly covered. The wounds covered with talc continued to ooze unabated; sulfanilamide and sulfathiazole likewise had no noticeable effect on this oozing. When sulfamethylthiazole was sprayed on the surface of the wound, however, an immediate effect was noted; a yellowish scum, closely adherent to the surface of the wound, seemed to form. Oozing simultaneously ceased and the wound remained dry unless this surface layer was rubbed from the wound; if this was done, bleeding would start again.

Wounds sprayed with powdered sulfapyridine responded at least as well as, and often better than, those sprayed with sulfa-

methylthiazole powder. The technic consisted of the spraying of a fine layer of powder over the surface of the wound. Bleeding and oozing usually were affected immediately, the surface of the wound becoming rather dry and covered with a thin, tenacious coating of the drug. This coating could easily be dislodged.

A solution of 40 per cent sodium sulfapyridine was tested on experimental wounds. Within three to five minutes the wounds appeared to be uniformly dry, and it was noted that the base of each wound was covered with what appeared to be a fine, silver-like precipitate. The wounds remained dry, and at the end of a half hour were still dry and covered by the film, which by this time had almost the consistency of scab formation.

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Toxic Reactions of the Sulfonamides

WHILE the ability of the sulfonamides to overcome many infections is unquestioned, it is just as true that they are capable of eliciting toxic reactions within the body organism and that the margin of safety between therapeutic effect and toxicity, particularly in the three older members of the group, sulfanilamide, sulfapyridine, and sulfathiazole, is not great. These toxic reactions are likely to occur in varying degrees at any time when the drugs have been administered and the physician must be ever alert to their appearance. The following chart is a guide to the commoner toxic symptoms.

The formation of *renal calculi* leading to a blocking of the urinary tract and *anuria* is always a possibility in sulfonamide therapy, particularly with sulfathiazole and less so with sulfapyridine, and must be rigidly guarded against. This possibility becomes even greater in warm climates, where sweat glands are more active, with a consequent decrease in the volume of urine excreted. To guard against the possibility of fatal anuria, it is most important to ensure a steady output of urine. Not only should fluids be pushed, but a record of the amount of urine passed should be kept and the quantity in 24 hours not allowed to drop below 1500 cc.

Sulfadiazine is often regarded as a practically safe member of the sulfonamide group of drugs, but it, too, is capable of causing an anuria by a mechanical blockage of the ureters. Such a case was reported by Mathé.¹ A review of the literature, says this author, reveals 15 cases of sulfadiazine anuria during the past year, and undoubtedly others remain unpublished. Ten were due to mechanical blockage of the ureters by crystals, and all but one were relieved by ureteral catheterization, that one receiving nephrostomy drainage. Four cases of anuria terminated in death due to acute toxic degenerative nephritis, resulting from

TABLE 1—TOXIC MANIFESTATIONS OF SULFONAMIDE COMPOUNDS

Manifestation	INCIDENCE				Clinical Significance and Procedure
	Sulfanilamide	Sulfapyridine	Sulfathiazole	Sulfadiazine	
Cyanosis	Common	Occasional (not severe)	Doubtful	Rare	Not serious
Nausea and vomiting	Common	Frequent	Occasional	Uncommon	If severe, discontinue drug
Headache and dizziness	Common	Common	Rare	Rare	Not serious
Psychoses, delirium	Uncommon	Uncommon	Very rare	Very rare	If severe, discontinue drug
Acidosis	Occasional	Not reported	Not reported	Unreported	Give alkali
Drug fever	Common	Uncommon	Common	Uncommon	May be serious, discontinue drug
Dermatitis	Common	Occasional	Common	Uncommon	May be serious, discontinue drug
Hepatic damage	Common	Rare	Rare	Unreported	May be serious, discontinue drug
Jaundice	Occasional	Rare	Rare	Rare	May be serious, discontinue drug
Moderate anemia	Common	Common	Occasional	Rare	Not serious; transfuse if necessary
Acute hemolytic anemia	Occasional	Rare	Not reported	Unreported	Serious; discontinue drug, give alkali transfuse
Leukopenia	Common	Common	Occasional	Rare	May be serious, discontinue drug
Granulopenia	Occasional	Occasional	Rare	Rare	May be serious, discontinue drug
Agranulocytosis	Occasional	Occasional	Very rare	Unreported	Serious, discontinue drug
Marked leukocytosis	Uncommon	Uncommon	Rare	Unreported	Not serious alone
Hematuria	Doubtful	Common	Common	Rare	If macroscopic, discontinue drug
Oliguria and nitrogen retention	Doubtful	Occasional	Occasional	Rare	Serious; discontinue drug, alkalize urine, force fluid
Arthritis	Not reported	Not reported	Occasional	Unreported	May be serious, discontinue drug
Conjunctivitis and scleritis	Not reported	Not reported	Occasional	Rare	May be serious, discontinue drug
Visual disturbances	Very rare	Doubtful	Not reported	Unreported	May be serious, discontinue drug
Stomatitis	Not reported	Rare	Rare	Unreported	May be serious, discontinue drug
Neuritis	Rare	Not reported	Rare	Unreported	May be serious, discontinue drug
Splenomegaly	Occasional	Doubtful	Occasional	Unreported	May be serious, discontinue drug
Hepatosplenomegaly and atelectasis	Rare	Not reported	Not reported	Unreported	May be serious, discontinue drug
Thrombocytopenic purpura	Not reported	Very rare	Not reported	Unreported	May be serious, discontinue drug

• From Spink, W. W., Bull. of the Minnesota Medical Foundation 36, 1941

calcifying necrosis of the tubules of the kidney. Two of these died in spite of ureteral catheterization.

The fact that sulfadiazine causes fewer gastrointestinal disturbances, continues Mathé, permits its ingestion by the average patient over a longer period of time than is usual with the allied group of drugs. In the sustained absence of toxic symptoms, the attending physician is prone to become overconfident and less alert to signs of potential renal damage, allowing complications to take place insidiously, which may vary from transitory hematuria to anuria and even death.

In 38 cases treated by Wright and Kinsey² with sulfadiazine, there were numerous cases of renal irritation, ranging from mild tenderness over the kidney to severe anuria, a greater frequency of renal complications than these authors had experienced with other sulfonamides. Seven patients had hematuria.

Louria and Solomon³ report on complete anuria following sulfadiazine therapy and reach the following conclusions:

1. If the urine output is good, the presence of crystals in the voided urine output should not be considered as indication for discontinuing the drug.

2. The appearance of gross blood in the urine at any time during administration of the drug should be an indication for discontinuing the drug.

3. Hematuria clears up promptly after the drug has been stopped.

4. No permanent renal damage has been observed in the cases in which recovery has been reported.

5. Obstruction of the urinary tract resulting from the deposition of crystals of the drug may be relieved promptly by ureteral catheterization and pelvic lavage.

6. Whether alkalization of the urine will deter crystal deposition in the urinary tract is still a moot point.

Adams⁴ reports *radiopaque membranous pyelitis* following sulfonamide therapy. Two cases were observed in which a calcareous radiopaque membrane formed on the epithelial surfaces

of the calices and renal pelvis of a kidney partially or completely blocked by a small ureteral calculus. Sulfathiazole in one instance and sulfadiazine in the other are thought to be at least partly responsible for this complication. Similar sulfonamide renal complications have not previously been reported. The membrane and kidney were available for study in one case and only the membrane, passed spontaneously, in the other.

Sulfathiazole and sulfadiazine may cause rapid formation of a nonsoluble, calcareous, radiopaque membrane on the epithelial surfaces of the calices and pelvis if there is an associated ureteral stasis, pyelonephritis, and alkaline urine. Therefore, these drugs should not be given indiscriminately in such cases but, if thought mandatory, every effort should be made to prevent the formation of such membranes by correcting ureteral stasis, maintaining renal drainage, improving the renal output and rendering the urine highly acid (pH 5.6 or less).

Early operative removal of such membranes is not indicated, for it is quite impossible to remove this material early either by nephrotomy or pyelotomy, when separation from the pelvis and calices is difficult. Later such membranes may separate spontaneously and are then more easily removed, or they may pass without operation.

Renal damage from sulfonamide therapy is due to two causes: (1) Mechanical obstruction and irritation by the crystals, and (2) toxic products of reactions to the drug. The drug should be stopped at the first sign of kidney complication. Fluids should be forced during the administration of sulfonamides, but the positive water balance should not be over 5000 cc. or edema of the brain with possible death may result. If oliguria drops to 500 cc., catheterization and cystoscopy should be performed, but one may wait 12 to 24 hours in the hope of diuresis. When the oliguria persists or if anuria develops catheterization should be done without delay and the catheters left in place until the urine is clear. The pelves should be washed frequently with warm water, normal saline, or sodium bicarbonate in sterile solutions, which relieves the extrarenal obstruction.

For intratubular obstruction, large quantities of fluid should be administered and, if necessary, hypertonic dextrose solution intravenously as diuretics. Magnesium sulfate predisposes to sulfhemoglobin formation and ordinarily should be avoided, but when the oliguria persists and no cyanosis has developed it may be resorted to intravenously. Mercuric and acid diuretics should not be used. The patient should be given an alkaline-ash diet and the urine kept alkaline with sodium bicarbonate. Fluids should be continued for several days after the kidneys have become normal and follow-up studies should be performed for residual or latent damage.

A complication of sulfonamide therapy has reached great importance during the present war. It has been found that pilots of aircraft are likely to crash while taking sulfonamides. Anoxia develops at much lower levels and there is an interference with depth perception. It was discovered that safety demands that pilots be grounded during and for a minimum of six days following the termination of sulfonamide therapy.

Foulger⁵ comments on this, quoting from the editorial correspondence in the *Journal of Aviation Medicine* (11:134, 1940):

"The use of sulfanilamide in the treatment of disease has increased our care of flyer problems. The British have found that a single dose reduces a pilot's ceiling about 5000 feet. We have had one death just after flying, from it, and one collapse. It is easily obtainable by anyone and, in fact, civilian doctors prescribe it without a thought of danger in relation to flying."

If a pilot flies above his ceiling (12,000 to 14,000 feet) without using oxygen he may pass rapidly through all the early stages of action of toxic chemicals to a state of circulatory collapse. When under treatment with sulfanilamide and similar drugs he has progressed well toward stages 4 and 5 even before flying, and a sudden decrease in oxygen supply may prove disastrous. In industrial medicine, the early action of toxic chemicals closely simulates oxygen deficiency and may lead to as drastic results as are experienced in aviation.

Further evidence of the action of sulfanilamide is given by Houghton and his collaborators:

"The mental and physical handicap of taking the drug in this dosage (2 to 3 Gm. daily) is greater than the psychological and physiological tests would indicate. Aside from the vomiting in two of the six cases, each of the subjects had a feeling of considerable malaise and mental incompetence. Such feeling was not conducive to good work in the laboratory during the period of the drug and *would undoubtedly impede the skilled activities of workers in industry or the military.* In emergency, however, a considerable amount of unskilled labor should still be possible, provided the subjects are free from vomiting."

An editorial note in J. A. M. A. on Mental Confusion from the Sulfonamides (119:1431 [Aug. 22] 1941) refers to a report of the Committee on Disability and Rehabilitation, Medical and Surgical Section, Association of American Railroads, in which "it is recommended that a patient, after receiving treatment of this type, should be free from work for 7 to 14 days following such administration, before being permitted to resume duties in either engine or train service. The possibility of serious mental confusion must be borne in mind, especially for those whose activities under circumstances of impaired judgment would be particularly hazardous to others.

"This would include many occupations in civil life and practically all those in military fields."

The effects of the "sulfa" drugs are rather lasting. We have record of at least one case in which a worker, having reached a state of circulatory collapse, failed to recover, with rest, in the normal period of two to six hours. He was under treatment with a "sulfa" drug merely because he showed an unexplained temperature rise. Actually, three weeks of rest were needed before a normal circulatory score was restored.

Nedzel⁶ reported experiments on white mice that showed sulfanilamide to be more toxic for them in April-May than in November-December. The same held true for the N. Y. 5 Cornell strain of *Streptococcus hemolyticus*.

The experiments with sulfanilamide were carried out on white mice in the following manner: From April 27 until May 18, 1942, inclusive, the same number of male and female animals were daily injected: (1) With sulfanilamide (first group); (2) sulfanilamide and streptococcus hemolyticus (second group); (3) streptococcus hemolyticus alone (third group). Each group consisted of eight male and eight female mice, or 16 altogether. Forty-eight was the number used daily, thus the total number of mice employed in the experiment was 864. The administered sulfanilamide was a one per cent w/v solution of distilled water, the temperature of the solution at the time of administration being 37.5° C. Each injection consisted of 1 cc. given subcutaneously, and four such injections were administered at intervals of one to one and one-half hours. The solution was supplied by Professor G. L. Webster of the College of Pharmacy and the streptococci were of the N. Y. 5 Cornell strain from Dr. M. V. Novak's collection. They were administered intraperitoneally in the amount of 0.1 cc. of brain broth culture, incubated at 37° C. for 24 hours.

TABLE 2

Injection	Time of Administration	Per Cent of Mice That Died			Difference Between Total Deaths
		Male	Female	Total	
Sulfanilamide	April—May	22.9	27.7	25.3	—5.6
	Nov.—Dec.	18.4	21.1	19.7	
Sulfanilamide and Strep. hemol.	April—May	63.2	68.7	65.9	—2.1
	Nov.—Dec.	65.1	62.5	63.8	
Streptococcus hemolyticus	April—May	71.5	75.0	73.3	—10.8
	Nov.—Dec.	59.8	65.1	62.5	

(Nedzel, A. J., *Urol. & Cutan. Rev.*)

Beginning November 17 until December 5, 1942, inclusive, experiments similar to those just described were repeated in exactly the same manner, the total number of mice used this time being 912. The results of both series of experiments are presented in Table 2.

The author does not attempt to apply his findings to humans, but points out that environmental factors, particularly atmospheric changes, bring about constant changes in our physiologic states. The decreased output of urine in the warmer months, mentioned previously, may be one factor in a greater toxicity of the sulfonamides in spring and summer, if such is true of humans.

That the sulfonamide drugs are capable of producing profound effects on the blood and blood-making organs has been known for some time. Some of the toxic effects reported have been acute granulocytosis, thrombopenic purpura, leukemoid reactions, and malignant neutropenia. Kracke and Townsend² made a study on the platelets in patients receiving sulfonamide drugs and reported their results as follows:

After observing three patients who had been treated with sulfathiazole and who subsequently had severe hemorrhages with ultimate death of all, we decided to investigate the effects of sulfathiazole on the platelets of patients who were receiving this drug in routine hospital practice.

It became necessary to select a satisfactory method for the estimation of platelets, and we first made platelet determinations by the three standard methods on 27 normal subjects. The platelets were estimated by the direct method, Fonio's method, and Olef's method. The blood for the three tests was taken from the normal subjects at the same time.

The direct method consists of puncturing the finger, wiping away the first drop of blood, drawing diluting fluid to the 0.5 mark, and then blood to the 1.0 mark in a red cell pipet and diluting fluid to fill the pipet. The fluid used was that of Rees and Ecker and is an aqueous solution containing sodium citrate and solution of formaldehyde with a small amount of brilliant

cresyl blue. After proper shaking of the pipet the counting chamber is filled and allowed to stand for 15 minutes on damp filter paper in a petri dish. The platelets are then counted. By this method the platelet count is usually between 250,000 and 350,000 per cmm. with extremes of 200,000 and 450,000 per cmm. The average platelet count on 27 normal subjects was 277,000 per cmm.

Fonio's smear method consists of puncturing the finger and at once placing a drop of 14 per cent magnesium sulfate over the puncture before the blood begins to flow. The blood then flows into the drop until the proportion is about one part of blood to one part of magnesium sulfate solution. A small drop is then placed on a slide and a thin smear is made. The magnesium sulfate is then wiped away and an ordinary red cell count is done by the usual technic. The smear is stained with Wright's stain, the platelets are counted with the oil immersion objective until 1000 red cells in various microscopic fields have been simultaneously enumerated. From these data the number of platelets is computed. In the group of 27 normal persons the average platelet count was 351,000 per cmm.

The third method used is known as Olef's paraffin cup method: The finger is punctured, the first drop of blood removed, and a drop of diluting fluid placed over the puncture. The formula for the diluting fluid used in Olef's method is given in Table 3. The blood then flows into the fluid in approximately equal amounts, and this mixture is received into a small paraffin cup which contains more of the diluting fluid. After being stirred with a paraffin-coated applicator and allowed to stand for two minutes, it is transferred to a slide in the form of a small drop sufficient to spread under a cover glass. After standing for 15 minutes, simultaneous counts are made of platelets and red cells and the number is then computed. By this method the usual range is 350,000 to 400,000 per cmm.

After this preliminary study, we decided to use Fonio's smear method for further studies. We based this decision on the fact that this method has the advantages of simplicity and, second,

of providing a permanent preparation. The results obtained by this method are within ten per cent of those obtained by the Olef method, which is probably more accurate. In any event, once a method has been chosen for routine purposes, it should be used to the exclusion of all others, so that platelet estimations will have comparative value. The individual counts in this study of 27 normal persons is given in Table 5.

Since the platelet counts may vary widely in the same individual from day to day, this has to be taken into account in an evaluation of the platelet fluctuations of patients under treatment. We decided to carry out daily platelet counts at approximately the same hour of the day on five normal subjects for a period of ten days. The results of this can be seen in Table 4.

It can be seen from this study that the platelet count may vary from 264,000 to 514,000 per cmm. in a normal person and in another subject from 264,000 to 407,000 per cmm., so it is obvious that great variations occur from day to day in the normal platelet count of the same individual, even when the counts are made at the same time of day with a standardized, carefully worked-out technic.

Platelet determinations were begun on patients who were admitted to the hospital for various causes and who were receiving or were to receive sulfathiazole therapy for a variety of conditions. This series included 61 patients, all of whom received therapy over a variable number of days, usually ranging from three days to eight days, and longer in an occasional instance. In a group of 23 of these 61 patients it was possible to obtain platelet counts before the institution of drug therapy. The results obtained on each patient can be seen in Table 6, and in Table 7 is a summary of the results.

These results indicate that there is but little significant difference between the platelet counts of the patients before drug therapy is given and the counts on the first, second, and third days of therapy, but in nearly all patients after therapy has been discontinued there is a fairly sharp rise in the number of platelets.

These averages are expressed in Table 8 and are presented graphically in Chart 1.

Thus, in 23 patients, the average platelet count on the day before drug therapy was 275,000, on the first day of therapy nearly 300,000, and on the second day of therapy 250,000, which

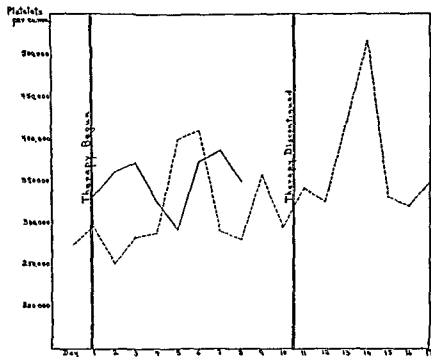


Chart 1—Average daily variation in the number of platelets in normal subjects (solid line; details in Table 4) and in patients during and after sulfathiazole therapy (broken line; details in Tables 6, 7, and 8).

(Kracke, R. R., and Townsend, E. W. *J. A. M. A.*)

was below the average level in the beginning. On the day that therapy was discontinued the average platelet level was nearly 350,000, but on the following day it rose to 525,000 and then again fell back to its normal level.

The results would seem to indicate that in patients receiving sulfathiazole therapy there is a slight depression of the platelets on the second day of therapy and a decided increase in the number on the day after therapy has been discontinued. Be-

cause of the wide variation in normal platelet counts, conclusions to be drawn from the platelet values of these 61 patients cannot be done with any degree of certainty. We can merely state that there seems to be a trend toward slight platelet depression after the institution of therapy and a considerable increase in the number of platelets after cessation of therapy. This trend, coupled with the two cases reported in this paper and those in the literature, indicates that in some instances platelet depression may occur to the point of thrombopenic purpura.

TABLE 3—THE DILUTING FLUID USED IN OLFF'S METHOD

Sodium metaphosphate (Howe & French)	1.0 Gm
Sodium chloride	0.4 Gm
Dextrose . . .	0.1 Gm
Sodium bicarbonate	0.1 Gm.
Brilliant cresyl blue	0.15 Gm
Distilled water	100.0 cc

(Kracke, R. R., and Townsend, E. W. J. A. M. A.)

TABLE 4—NORMAL DAILY VARIATIONS IN PLATELETS IN HEALTHY ADULTS

Normal Subject	Daily Platelet Count (in Thousands)									
	1	2	3	4	5	6	7	8	9	10
1	514	480	429	362	274	309	300	349	356	264
2	264	367	407	284	319	395	507	379	514	451
3	270	242	427	288	251	366	320	307		
4	307	364	275	318	336	432	431			
5	322	358	331	388						

(Kracke, R. R., and Townsend, E. W. J. A. M. A.)

Acute agranulocytosis due to the administration of sulfanilamide has been reported by Long, Haviland, Edwards, and Bliss⁸; sulfapyridine by Dolgopel and Hobart⁹; sulfathiazole by Kennedy and Finland,¹⁰ and sulfadiazine by Curry.¹¹ Johnson¹² reports the following case due to succinylsulfathiazole:

TABLE 5—PLATELET DETERMINATION BY THREE METHODS
IN NORMAL SUBJECTS

<i>Subject</i>	<i>Direct Method</i>	<i>Fonio's Method</i>	<i>Olef's Method</i>
1	212,000	443,520	485,100
2.	259,000	291,200	565,760
3.	325,000	445,410	456,520
4.	238,000	353,760	378,210
5.	274,000	367,920	443,520
6	224,000	481,320	492,780
7.	200,000	303,750	252,350
8.	235,000	378,020	378,020
9.	224,000	374,000	204,250
10.	209,000	351,000	369,000
11	270,000	298,960	319,160
12.	312,000	330,600	364,800
13.	334,000	374,320	351,260
14	265,000	340,180	407,420
15.	391,000	419,220	493,200
16.	299,000	252,450	362,610
17.	219,000	202,350	276,900
18	244,000	283,930	291,830
19	367,000	450,300	677,150
20	209,000	300,300	373,230
21.	420,000	525,200	463,200
22	258,000	300,000	423,150
23	243,000	337,400	404,880
24	428,000	501,000	527,940
25	342,000	333,000	397,600
26.	180,000	240,000	350,620
27	294,000	328,400	351,740
Averages	277,000	351,000	400,000

(Kracke, R. R., and Townsend, E. W. *J A M A*)

Acute agranulocytosis was fatal to a youth who had received a total of 159 Gm. of succinylsulfathiazole over a period of 17 days. The patient had demonstrated reactions on two previous occasions while taking sulfathiazole and concomitantly receiving injections of killed typhoid bacilli. Though the first episode of fever might have been due to the injection of killed typhoid bacilli, the second febrile reaction was undoubtedly due to sulfa-

TABLE 6—PLATELET COUNTS IN PATIENTS UNDER
SULFATHIAZOLE THERAPY

Patient	Day of Therapy									
	0	1	2	3	4	5	6	7	8	9
1*	..	700	900	600	660	720	650	660	840	...
2	320	300	320	300
3	.	340	350	370	360	420	470
4	.	370	410	390	450	630
5	..	570	510	480	340	420
6	.	400	370	500	430
7	.	380	400	340	370
8	290	340	340	375
9	..	320	500	450	590	530	510
10	..	280	400	460	320	350
11	...	270	250	240	280	380
12	.	490	500	630	910	610	500	.	.	.
13	280	280	220	280	210	220
14	.	240	320	330
15	.	260	470	330
16	..	420	360	500	400
17	350	410	380	410
18	.	350	420	360
19†	.	280	290
20	420	300
21	330	300	290	230	300	310	220	.	.	.
22§	..	270	150	300	200	260	300	290	270	.
23	180	200	350	300	280
24	210	230	210	220
25	.	130	230	260
26	...	290	300	290	350
27	340	360	250	230	260	300	260
28	380	310
29	...	250	160	260	210
30	.	280	240	240	260
31	...	450	340	330
32	280	290	300	300
33	220	300	190	230
34	170	200	220	200
35	160	200	210	190	200
36	230	320	280	290
37	300	350	300	280
38	.	311	149	249
39	...	308	304	251	167	761
40	65	196

(Krschke, R. R., and Townsend, E. W. J. A. M. A.)

TABLE 6—PLATELET COUNTS IN PATIENTS UNDER SULFATHIAZOLE THERAPY
(Continued)

Patient	Day of Therapy									
	0	1	2	3	4	5	6	7	8	9
41	.	.	305	253
42†	.	.	341	235
			317	204						
43	.	.	299	236	384	230	.	687	362	267
44	.	.	149	217	256
45	..	.	289	397	354	285	.	301	239	232
46		.	357	121	426		
48	.		313	197	.	326	.			..
49			640	439	.	527	862	641	.	.
50	..		427	481	273	550	249		..	.
51			185	205	473	258			.	.
52			199	159	280		283	229	281	364
53		375	289	280		586	528			
54			330	229	412					
55		330	217	199	247	.				
57		263	287		293	170	262	553		
58		312		245	215					
47*			617	455	676	.	468	525	285	740
56		524	452		332	564	512	385	427	572
59	.	448	.	270	334	518				
60	.	290	511	869	708	747	443			
61	224	271	161		277

*Patients 1 through 18 and 47, 56, 59, 60 and 61 were infants and children aged 4½ months to 12 years.

†Patients 19 through 58 as they appear in the table were aged 13 to 81 years. Patients 34 through 37 were over 70 years of age.

‡Patient 42 received sulfathiazole for two days, had chemotherapy discontinued for five days, and received a second course of the drug for three days.

§Patient 22 was continued on sulfathiazole therapy for ten days and showed a platelet count of 400,000 on the ninth and on the tenth day.

(Kracke, R. R., and Townsend, E. W. *J. A. M. A.*)

thiazole. On the second day following the administration of succinylsulfathiazole a fever developed which persisted for four days. As succinylsulfathiazole is partially hydrolyzed to sulfathiazole, this febrile response no doubt was due to a sensitization to sulfathiazole, which sensitization manifested itself during the

TABLE 7—AVERAGE PLATELET COUNTS IN PATIENTS WITH
SULFATHIAZOLE THERAPY

	<i>Day of Therapy</i>										
	0	1	2	3	4	5	6	7	8	9	10
Children	357	302	376	419	476	460	506	457	717	..	.
Adults.	257	296	253	384	290	401	411	293	283	357	296

(Kracke, R. R., and Townsend, E. W.: J A M A.)

TABLE 8—AVERAGE PLATELET COUNTS IN RELATION TO DAYS
AFTER DISCONTINUANCE OF SULFATHIAZOLE

	<i>Day After Discontinuation</i>						
	1	2	3	4	5	6	7
Children	417	495	622	821*	554		
Adults.	343	326	421	517	333	322	352

*Count made in one case only.

(Kracke, R. R., and Townsend, E. W.: J A M A.)

second course of administration of the drug. However, with continued administration of succinylsulfathiazole the temperature, pulse, respiratory rate, and white blood cell count became normal, so it was believed that this intolerance to the drug had ceased. For eight days the patient was asymptomatic with a normal temperature and white blood cell count. His final febrile response began with the injection of killed typhoid bacilli. Acute agranulocytosis began when he had taken 159 Gm. of succinylsulfathiazole and continued to termination in spite of treatment which had cured attacks of acute agranulocytosis in rats fed succinylsulfathiazole. Sensitivity has been shown to be present not only when there has been an interruption in the course of medication, but also when there has been a prolonged administration of large doses of the drug. Both of these conditions were present in this case.

A second course of sulfathiazole must be given cautiously, as evidenced in a report by Lyons and Balberor,¹³ who show that *febrile reactions* may result. Although such febrile reactions may not in themselves present any danger, they cannot be differentiated from the fever caused by the infection for which the sulfonamide has been given and may tempt the physician to give larger doses of the sulfonamide. The authors' conclusions follow:

1. Nineteen of 53 patients (36 per cent) to whom sulfathiazole was readministered experienced a *febrile reaction* shortly after the beginning of the second course, although no fever attributable to the drug was experienced during the first course.

2. Febrile reactions were characterized by a sharp rise in temperature from 102° to 106° F. and were often accompanied by chills and were associated with prostration and weakness.

3. Eight of ten patients who had a thermal reaction with the second course experienced a similar reaction when given a third course of the drug. Certain selected patients had multiple febrile reactions when given repeated courses of sulfathiazole.

4. No patient exhibited a thermal reaction earlier than the *ninth day*, although the *second course* in some instances was started as early as the fifth day after the initial contact with the drug.

5. A febrile reaction occurred with the readministration of the drug, although the interval between courses was prolonged to as long as 41 days.

6. In a series of 200 consecutive routine hospital cases, in which a single course of sulfathiazole was administered, a drug fever developed in only five. None of these occurred before the seventh day. If the cases in which the drug was given for less than seven days are eliminated, the incidence of drug fever in this series is a little over ten per cent.

7. It is suggested that the fever is due to a drug hypersensitivity and that the incidence of this reaction is enhanced by an interval between courses in contrast to the continuous administration of the drug. (See also page 78.)

8. The patients in this series who exhibited a thermal response to readministration of sulfathiazole were able to tolerate sulfanilamide or sulfapyridine without fever.

Green and Steckel¹⁴ report a case showing this fever reaction to a second course of sulfonamide therapy:

D. K., a white male aged 30, was admitted to the hospital on June 22, 1942, stating that pustular lesions had appeared on the skin of his legs about three weeks before admission. These had subsequently increased in number and size. He had no other complaint.

Physical Examination: The patient was a well-developed, well-nourished soldier, afebrile, obviously not acutely ill. The only abnormal finding consisted of a large number of typical ecthyma lesions almost equally distributed on the anterolateral aspect of both lower extremities.

Laboratory Examination: The urine was normal in all respects. The blood showed 4,250,000 erythrocytes per cmm. hemoglobin of 90 per cent, and a white count of 7900 with 65 per cent polymorphonuclears, 32 per cent lymphocytes, 2 per cent monocytes, and 1 per cent eosinophiles. The Kahn was negative. Blood sugar determinations were within normal limits, as was the basal metabolic rate. *Staphylococcus aureus* was cultured from pus obtained from the lesions.

Course: Sulfathiazole was administered orally on the day of admission in divided doses totaling 5 Gm., with four 1-Gm doses ordered given at four-hour intervals daily until otherwise changed or discontinued. Local applications of five per cent sulfathiazole ointment to the lesions were initiated at the same time. The following day, June 23, after two doses of sulfathiazole, or after a total of 7 Gm. orally, the patient suddenly developed a fever, which rapidly mounted to 102° F., and was accompanied by a generalized morbilliform dermatitis. Sulfathiazole both orally and locally was ordered discontinued, but through oversight the ointment applications were continued. Careful questioning revealed that the patient had never before

This question of *sensitivity* is dealt with in the following editorial which appeared in the J. A. M. A.:¹⁵

A chemical theory as to the mechanism of acquired sensitivity to sulfonamide compounds is supported by a study made by Wedum of the Department of Bacteriology, University of Cincinnati, on the antigenicity of sulfonamide azoproteins.

Statistical evidence recently published by Lyons and Balberor indicates that approximately one-third of all patients treated with sulfonamide drugs develop a sensitivity to these drugs sufficient to interfere with their subsequent use on these patients. Other investigators have shown that this sensitivity usually develops about nine days after the first administration of the drug and may persist for at least two years. The dominant symptom of the resulting "sulfonamide shock" is a prompt febrile reaction, often reaching higher than 104° F., accompanied by chilliness, erythema, pruritus, and conjunctival injection. Attempts to diagnose the hypersensitive state by patch, scratch, or intradermal tests, or by passive transfer of the patient's serum have almost invariably given negative results. *In vitro* serum reactions are also negative. Acquired sulfonamide sensitivity to derivatives must therefore differ essentially from the familiar clinical picture of allergy or anaphylaxis.

In order to determine the physiologic mechanism of this acquired sensitivity, attempts were made by the Cincinnati biochemist to sensitize guinea pigs to sulfanilamide, sulfapyridine, and sulfathiazole. Each animal received three combined intradermal and intraperitoneal doses of the drug at intervals of three days. The animals were tested by an intradermal injection of an aqueous solution of each drug 29 days after the last dose. Local

skin reactions were not noted. To each of a second group of presumably sensitized guinea pigs was given a shocking dose of the same drug intracardially. Constitutional anaphylactic reactions did not occur. A third group of treated guinea pigs gave negative *in vitro* reactions on specific precipitin titrations. Evidently sulfonamide compounds are in themselves nonantigenic and cannot serve as sensitizing, immunizing, or testing reagents. Theoretically, the only way these drugs could function as antigens, therefore, would be as haptens conjugated with a colloidal protein carrier.

In order to confirm this deduced hapten function, the three sulfonamide compounds were each conjugated with egg white, beef serum, human serum, or rabbit serum by the Landsteiner technic. The resulting sulfonamide azoproteins were used as sensitizing agents for a series of guinea pigs. Twenty-nine days after the final sensitizing dose the guinea pigs all gave positive reactions to intracutaneous tests with the same protein conjugates, in some cases the reaction being sufficiently severe to cause local necrosis. Cross sensitization was noted with these hapten conjugates. Sulfanilamide azo beef proteins, for example, gave positive reactions on guinea pigs sensitized with sulfanilamide azo human serum proteins and *vice versa*. Reactions with the homologous protein, however, was always strongest.

A second group of similarly sensitized guinea pigs was tested for constitutional anaphylaxis by intracardiac injections. Lethal anaphylactic reactions were noted in approximately a third of the cases, with an equal number of sublethal shocks. Here also cross reactions were recorded, though less numerous than in the previous intracutaneous tests.

Numerous rabbits received repeated injections with the hapten conjugates. All rabbits yielded precipitins for homologous chemoproteins. Cross reactions were noted. There was a suggestion of a serologic gradient of specificity among the three sulfonamide compounds tested, sulfathiazole having the broadest base of heterogenicity. Sulfanilamide was most highly specific.

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These findings are in accord with previously reported clinical experience.

Wedum concludes that there is no evidence that the simple uncombined sulfonamide compounds can serve either as sensitizing or as testing antigens. Animals presumably sensitized with these simple chemicals do not respond when tested with corresponding hapten protein conjugates. Animals demonstrably sensitized to the hapten conjugates also give negative reactions with the uncombined sulfonamide compounds. Whether or not it would be possible to desensitize or fully immunize guinea pigs against these hapten conjugates, and the effect of such desensitization on the therapeutic efficiency of the uncombined sulfonamide drugs, have not yet been reported from the Cincinnati laboratory.

The *jaundice* which sometimes appears following the use of sulfanilamide is usually hemolytic, but in about 0.6 per cent of the cases receiving sulfanilamide it is ascribed to *hepatic damage*. The theory has been advanced that in this latter group of cases the liver has already been damaged prior to the administration of sulfanilamide, and the drug causes the preëxisting hepatic damage to progress to a stage from which regeneration is impossible.

* Machella and Higgins¹⁰ attempted to test this hypothesis experimentally on rats. Sulfanilamide was administered to: (1) A group of animals in which hepatitis had been induced by means of carbon tetrachloride; (2) a group in which hepatitis was being induced by means of carbon tetrachloride; (3) a group receiving alcohol; (4) a group in which obstructive jaundice had been induced by ligation of the common duct.

The conclusion of the authors from their experiments were that the administration of sulfanilamide in moderately toxic doses does not increase the damage produced in the liver of a rat by carbon tetrachloride, and that it does not impede regeneration of the liver after hepatitis has been induced by carbon tetrachloride.

These experimental data, they say, appear to be in accord with slowly accumulating clinical data, which show that when sulfanilamide and allied compounds were administered to patients who had hepatic damage there were no apparent significant increases of hepatic dysfunction. However, they do not shed any light on the question why, when patients receive sulfanilamide, hepatitis develops in some cases but not in others. A depression of hepatic function among patients receiving sulfanilamide has been reported.

Skin reactions resulting from sulfonamide therapy are dealt with in the Section on Dermatology.

Sulfonamide Fatalities: Toxic reactions from sulfonamide therapy may result in death and Sutliff, Helpern, Griffin, and Brown¹⁷ have reviewed the sulfonamide deaths which occurred in New York City in 1941. Although few individual physicians, they say, treat enough patients with sulfonamide drugs to make the risk of fatalities approach certainty within periods of one or even several years, every physician using sulfonamide drugs runs some risk of observing such a fatality among his own patients. The serious problem presented by the combination of great therapeutic value with definite toxic hazards must be faced by the profession.

The frequency of fatal sulfonamide toxicity makes it necessary to consider the possibility of reducing their numbers. Measures are being actively sought to avoid serious toxic reactions, but so far with little success. It seems possible, however, that the use of less drug in each case would prevent the occurrence of some reactions. Emphasis on early diagnosis of susceptible infections and early treatment, with resulting more rapid and more complete therapeutic effects, is the most desirable method of decreasing the amount of drug needed in each case. It is not advisable to change standard dosage schedules which are known to be successful, since they are based on experimental demonstration of the necessity for certain minimum blood levels of the drugs for maximum therapeutic effect.

TABLE 9—CASES OF FATAL SULFONAMIDE TOXICITY REPORTED IN NEW YORK CITY IN 1941

A. TOXICITY PRIMARILY AFFECTING THE BLOOD CELLS AND BLOOD FORMING ORGANS							
Patient	Age	Sex	Principal Reaction	Drugs	Total Amount Gm.	Disease Treated	Cause of Death
1. A. G.	53	♂	*Agranulocytosis	Sulfanilamide	103	Infected foot (diabetic gangrene)	Agranulocytosis
2. C. H.	50	♂	*Agranulocytosis	Sulfanilamide (33.32 Gm.) Sulfapyridine (84.0 Gm.) Sulfathiazole	117	Bacterial endocarditis (Strept. viridans)	Agranulocytosis, bacterial endocarditis
3. L. W. V.	68	♂	*Agranulocytosis	Sulfathiazole	98	Cystitis	Agranulocytosis, prostatic hypertrophy (operation), peritonitis
4. C. S.	44	♀	*Agranulocytosis	Sulfanilamide (in wound 60.0 Gm.) Sulfathiazole (24.5 Gm.)	84	Infected operative wound cystitis	Agranulocytosis, cancer of sigmoid (operation), bronchopneumonia
5. R. F.	15	♂	*Agranulocytosis	Sulfanilamide (53.1 Gm.) Sulfathiazole (intravenous 3.8 Gm.)	57	Rheumatic fever inactive	Agranulocytosis, septicemia, Staphylococcus aureus, pneumococcus type 3
6. A. M.	19	♀	Agranulocytosis	Sulfanilamide	50	Pharyngitis	Agranulocytosis, bronchopneumonia
7. F. M.	65	♀	Agranulocytosis	Sulfapyridine	16	Upper respiratory infection	Agranulocytosis
8. R. E. M.	60	♀	Agranulocytosis	Sulfathiazole (12.0 Gm.) Neopristin (17.0 Gm.)	29	Tuberculosis	Agranulocytosis, aminopyrine 7 Gm.
9. C. G.	43	♂	*Acute hemolytic anemia, hemoglobin nephrosis	Sulfanilamide	10	Infected accidental wound	Acute hemolytic anemia, hemoglobin nephrosis, pneumonia
10. M. R.	45	♂	Aplastic anemia	Sulfathiazole	7	Lobar pneumonia, type 19	Aplastic anemia, type 18 pneumonia, bacteremia
11. B. H.	66	♀	*Purpura hemorrhagica	Sulfathiazole	12	Lobar pneumonia	Purpura hemorrhagica
12. N. F.	60	♀	*Thrombocytopenic purpura	Sulfathiazole	24	Infected operative wound	Thrombocytopenic purpura (operation), Staph. aureus, sepsis

*Diagnosis well established.

* Diagnosis well established

TABLE 9—Continued

B. TOXICITY PRIMARILY AFFECTING THE KIDNEY					
Patient	Age	Sex	Principal Reaction	Drugs	Total Amount Gm
13 C. T. V.	45	♀	*Crystalline urinary concretions	Sulfathiazole	35
14 H. K.	60	♂	*Crystalline urinary concretions	Sulfathiazole	44
15 R. N.	15	♀	*Crystalline urinary concretions	Sulfathiazole	18.5
16 C. N.	80	♀	*Crystalline urinary concretions	Sulfadiazine	128
17 L. C. D.	65	♂	Acute nephrosis	Sulfathiazole	28
18 M. McG	56	♀	Acute nephrosis	Sulfapyridine	14
19 F. R.	48	♂	Azotemia	Sulfathiazole (intravenous)	24
20 W. J. D.	57	♂	Azotemia	Sulfathiazole	40
21 N. L.	65	♂	Azotemia	Sulfadiazine	27
22 L. K.	56	♀	Azotemia	Sulfapyridine	31
23 P. M.	39	♀	Azotemia	Sulfapyridine	12
24 G. B.	70	♂	Azotemia	Sulfathiazole	29
C. TOXICITY PRIMARILY AFFECTING THE SKIN AND OTHER TOXIC MANIFESTATIONS					
25 E. A. W.	31	♀	*Dermatitis exfoliativa	Sulfapyridine	24
26 J. M.	42	♂	Dermatitis hyperpyretica	Sulfathiazole (intravenously 6 Gm.)	70
27 R. T.	59	♂	Dermatitis, pulmonary edema	Sulfathiazole (38 Gm.)	88
28 M. L.	11 mos	♀	Convulsions	Sulfapyridine (11 Gm.) (39 Gm. intravenously)	9
				Sulfathiazole (7.2 Gm.) Sulfapyridine (1.2 Gm.) (0.5 Gm. intravenously)	
*Diagnosis well established.					
				(Sutcliffe, E. D., et al.: J. A. M. A.)	

TABLE 10—NUMBER OF DAYS ELAPSING BEFORE THE DEVELOPMENT OF TOXICITY AND DEATH

A. TOXICITY PRIMARILY AFFECTING THE BLOOD CELLS AND BLOOD FORMING ORGANS							
Patient	Principal Reaction	Other Toxic Symptoms	Drugs	Days of Treatment	Number of Days from First Dose of Drugs to		
					First Toxic Symptoms	Principal Toxic Reaction	Death
1. A. G.	Agranulocytosis .	Fever,* dermatitis	Sulfanilamide	20	16	21	23
2. C. H.	Agranulocytosis.	Fever (due to endocarditis ?)	Sulfanilamide (8 days) Sulfapyridine (23 days)	31 (82-day period)	-	88†	94
3. L. W. V.	Agranulocytosis . .	Fever,* dermatitis	Sulfathiazole	17	17	22	28
4. C. S.	Agranulocytosis	Fever,* dermatitis	Sulfanilamide (in wound 37 days) Sulfathiazole (7 days) Sulfanilamide (31 days in 32 days)	37	31	35	37
5. R. F.	Agranulocytosis	Fever, angina (due to sepsis)	Sulfathiazole (extra-venously 1 day) Sulfanilamide	32 (in 35-day period)	29	32	35 35
6. A. M.	Agranulocytosis .	Fever (due to broncho-pneumonia ?)	Sulfapyridine	16 (19-day period)	-	23	25
7. F. M.	Agranulocytosis	Fever (due to respiratory infection ?)	Sulfapyridine	3	-	2	14
8. R. E. M.	Agranulocytosis . . .	Fever (due to tonsillitis ?)	Sulfathiazole (2 days) Neoprontol (3 days)	5	-	4	9
9. C. G.	Acute hemolytic anemia. .	None	Sulfanilamide	1	-	1	10
10. M. R.	Aplastic anemia . . .	Fever (due to pneumonia ?)	Sulfathiazole	2	-	6	23
11. B. H.	Purpura hemorrhagica .	None	Sulfathiazole	2	-	5	7
12. N. F.	Thrombocytopenic purpura	Fever (due to sepsis ?)	Sulfadiazine	6	-	6	8

TABLE 10—Continued

B. TOXICITY PRIMARILY AFFECTING THE KIDNEY						
13. C. T. V.	Crystalline urinary concretions...	Fever,* dermatitis, chill, delirium, convulsions	Sulfathiazole	8	7	9
14. H. K.	Crystalline urinary concretions	Fever,* chill,* dermatitis, sulfathiazole retention	Sulfathiazole	10	8	11
15. R. N.	Crystalline urinary concretions.	General aches and pains,* vomiting, delirium, fever,* convulsions	Sulfathiazole	31	30	32
16. C. N.	Crystalline urinary concretions*	Sulfadiazine retention	Sulfadiazine	22	.	22
17. E. C. D.	Acute nephrosis...	Fever,* chill,* dermatitis	Sulfathiazole	13 (15-day period)	11	16
18. M. McG.	Acute nephrosis...	Fever,* dermatitis, delirium	Sulfapyridine	4 (5-day period)	3	6
19. F. R.	Azotemia...	...	Sulfathiazole (intravenously)	5	.	2
20. W. J. D.	Azotemia...	Urticaria*	Sulfathiazole	5	5	7
21. N. L.	Azotemia...	Oliguria,* severe emesis	Sulfadiazine	6	5	6
22. L. K.	Azotemia...	Oliguria	Sulfapyridine	8	..	7
23. P. M.	Azotemia...	Cema*	Sulfapyridine	3	3	7
24. G. B.	Azotemia...	Fever,* dermatitis,* sulfathiazole retention	Sulfathiazole	6	7	12
C. TOXICITY PRIMARILY AFFECTING THE SKIN AND OTHER TOXIC MANIFESTATIONS						
25. E. A. W.	Dermatitis exfoliativa.	Fever	Sulfapyridine	16 (19-day period)	.	23
26. J. M.	Dermatitis, hyperpyrexia ..		Sulfathiazole (intravenously on 11th day)	11	.	11
27. R. P.	Dermatitis, pulmonary edema	Jaundice	Sulfathiazole (7 days), Sulfapyridine (9 days, some intravenously)	15	.	15
28. M. L.	Convulsions.	Hyperpyrexia (due to bronchopneumonia †)	Sulfathiazole (9 days) in 11 days	10 (in 13-day period)	..	12
			Sulfapyridine (2 days) (0.5 Gm. intravenously 11th day)			13

* Indicates first toxic symptoms observed † Sulfanilamide ‡ Sulfapyridine

(Sulliff, E. D., et al.: J. A. M. A.)

Even after the onset of toxic symptoms, measures may be taken to reduce the number of fatalities. Early recognition of serious toxic symptoms, followed by prompt cessation of drug therapy, is of considerable importance. Symptomatic therapy, such as transfusion in blood dyscrasias, alkalization of urine in hemoglobin nephrosis, and instrumental relief of gross urinary tract obstruction may also save some patients. But symptomatic therapy can be only partially successful, and some fatal toxic reactions will continue to occur. It is to be hoped that biochemists will develop therapeutic agents which are less toxic or devise ways of lessening the toxic effects of present drugs.

The frequency of fatal sulfonamide toxicity makes it necessary to consider whether the beneficial results of sulfonamide drug therapy are sufficient to justify the continued use of these drugs as now practiced. Since low fatality rates have been shown to result from sulfonamide therapy in many infections, the changes in reported deaths from diseases for which sulfonamide drugs are now used should give some indication as to whether lives are actually being saved. Striking changes have occurred in the number of reported deaths in New York City from the 14 following infections for which sulfonamide drugs are used to treat the infection itself, to treat predisposing conditions, or to treat serious complications: Cerebrospinal (meningococcic) meningitis, scarlet fever, erysipelas, measles, meningitis (not meningococcic), diseases of the ear and mastoid process, pneumonia (all forms), empyema, diseases of the pharynx and tonsils, appendicitis, abortion with mention of infection, infection during childbirth and through the puerperium, phlegmon and acute abscess, and osteomyelitis and periostitis. It is estimated that if the average mortality rate from these causes of 137.5 deaths per 100,000 of population during the five years 1932 through 1936, before the introduction of sulfonamide drugs had persisted through 1911, 10,341 deaths would have occurred instead of the 4475 reported, a difference of 5866 deaths. While the number of deaths from many of these diseases was decreasing before this period and were subject to other influences than

the introduction of sulfonamide drugs, it may reasonably be assumed that some part of the decrease in each of these conditions was due to sulfonamide therapy. It is safe to say that the number of lives saved by sulfonamide drugs in New York City in 1941 was very much greater than the number of deaths caused by the toxic action of these drugs.

Bacterial endocarditis presents a special application of sulfonamide drug treatment, because the disease is almost invariably fatal and therefore fatalities which appear to be due to the drug are also usually considered due in part to the disease. The number of recoveries resulting from drug therapy is, however, small, and it would be well to demonstrate that the number of recoveries from sulfonamide treatment of bacterial endocarditis is greater than the number of cases in which serious terminal toxic reactions occur in evaluating drug therapy of this disease.

In acute gonococcic infections, few or no lives are saved; but since 85 per cent of the cases result promptly in cure by one course of a relatively small dose of sulfathiazole, the prospect of eradicating this disease is considered well worth the few serious toxic reactions that result from sulfonamide treatment.

Our present satisfactory experiences with sulfonamide treatments encourage their extension to other diseases. Such extensions should be based on therapeutic trial carried out to assemble clear information as to therapeutic and toxic effects. Such extension may, however, be directed toward the prevention of sequelae of the disease under treatment, the prevention of infections resulting from operative procedures, the prevention of recurrences of disease such as acute rheumatic fever or toward the cure of the carrier state for various pathogenic bacteria. It is essential that such preventive use of sulfonamide drugs should be considered successful only when fatal toxic reactions are entirely avoided.

This study of fatal toxic reactions, following the use of sulfonamide drugs in one year in New York City, presents no evidence that would modify the course that is being pursued

in the routine use and in the experimental extension of the use of sulfonamide drugs. The benefits derived from this course are much greater than the risk of serious toxic reactions incurred.

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Tests for Sulfonamides

BOGEN¹ presents the following report on a simple test for sulfonamides in the urine.

An easy, rapid, and reliable test for sulfonamides is of great value. The drugs are never present in the body unless previously taken. Such administration may not be known to the patient or to the medical officer who is to care for him. Inability, ignorance, or culpability may keep the patient from reporting previous use, while the frequent separation of men from their own medical officers and records, especially in the field, makes it impossible to rely upon their histories. Whenever treatment with such a drug is undertaken, it is important to know whether the patient has already taken some, so as to give adequate but not excessive dosage. Flavoring of sulfonamide tablets with peppermint may lessen the danger of overdosage in the unconscious or unknown wounded. *More persistent, reliable, sensitive, and specific information can be obtained by a simple qualitative test of the urine.*

Sulfonamides may be detected, and their concentration accurately determined, by Marshall's test, but this procedure is too elaborate and exacting for routine or field use. Attempts have been made to simplify it, mainly at the expense of precision. Other tests have been proposed, depending upon different reactions. *The simplest of these is the lignin test.*

Lignin Test: The lignin test is extremely quick and easy. A drop of urine is placed on a piece of wood-pulp paper and a drop of hydrochloric acid added. That is all. If as little as 0.01 per cent sulfonamide is present, a yellow color appears, which deepens to an orange with higher concentrations. Nothing apt to occur in the urine gives a false positive test.

More than 500 substances have been tested at the Norfolk Naval Hospital to see if they would give a yellow or orange color

with wood-pulp paper and hydrochloric acid. Some, as the dye-stuffs, had so strong a color themselves as to preclude reading the tests. A few others, as nitric acid, caused yellowing or charring of the paper in concentrated form, but gave no such color when diluted. No positive tests were obtained with inorganic substances, alcohols, aldehydes, acids, alkaloids, hormones, vitamins, etc.

A positive reaction was obtained with sulfanilamide, sulfapyridine, sodium sulfapyridine, sulfathiazole, sodium sulfathiazole, sulfadiazine, and sulfaguanidine, but with prontosil and neoprontosil it was obscured by the color of the dye itself. A positive test was also obtained with aniline, benzidine, hydrazine, naphthylamine, *o*-tolidine, paradimethylaminobenzaldehyde, para-aminobenzoic acid, sulfanilic acid, and the local anesthetics, procaine, benzocaine, and larocaine. None of these, however, has been encountered in urine in concentrations sufficient to give a positive test.

False positive reactions may be obtained similarly with Marshall's, Werner's, and other sulfonamide tests. Though these substances are not apt to appear in the urine, they have caused serious confusion in connection with blood, spinal fluid, pleural effusions, and other body fluids. This error may be prevented by omitting deep infiltration with procaine when a sulfonamide determination is to be made, or by using cocaine, nupercaine, holocaine, or metyrcaine, which do not give the test, instead of procaine, pontocaine, benzocaine, or larocaine, which do. The procaine may also be eliminated from the specimen by the use of Mayer's reagent, which precipitates it while leaving the sulfonamide unaffected.

The fact that acidified aniline products or aromatic amides produced a yellow color in contact with wood has been known for a century, but the essential chemical reaction responsible for this change is still obscure. The behavior of sulfonamides is only one instance of this general phenomenon, but fortunately the other substances which may duplicate it do not occur in the urine.

Any product containing wood pulp, such as paper towels, toilet paper, newspaper, cheap magazine paper, rough pencil-writing pads, sawdust, etc., at once presents a positive test, a bright yellow or orange color when touched with a drop of hydrochloric acid and sulfonamide. A similar color is elicited in the absence of wood pulp by adding hydrochloric acid and sulfonamide solution to Ehrlich's reagent, paradimethylamidobenzaldehyde. A yellow, but not the orange tint, could be obtained by adding the sulfonamide in hydrochloric acid to vanillin. No yellow color could be elicited in this manner from more than 500 other substances which were tested at the Norfolk Naval Hospital. Filter paper, linen writing paper, or bond typewriter paper, absorbent cotton, cellucotton, or Kotex, etc., were uniformly negative.

The active reacting material in fresh fir sawdust, giving the yellow color with sulfonamide in hydrochloric acid, is completely insoluble in acids, alkalis, alcohols, etc. Accordingly, it cannot be vanillin, Ehrlich's reagent, or other soluble substance. It is probably the insoluble constituent of wood cells, lignin, a cyclic unsaturated compound, whose exact formula has not been established, but may be a polymer of coniferyl alcohol.

The results of the lignin test can be read as follows: Light yellow is read as 1-plus, corresponding to about 0.01 per cent sulfonamide; a deep yellow as 2-plus, corresponding to about 0.05 per cent sulfonamide; an orange yellow as 3-plus, corresponding to about 0.1 per cent sulfonamide, and an orange color at 4-plus, corresponding to 0.5 per cent or more of sulfonamide.

A Bedside Test for Sulfapyridine: Bullowa and Ratish² recommend a simple test, which enables one to make sure that a sufficient amount of sulfapyridine is in the patient's blood to be effective in combating infection. The test can be done in a modestly equipped laboratory which many practicing physicians now have. No complicated apparatus or unusual technic is required. The test is a modification of Marshall's test and is based

on extraction of sulfapyridine from the blood with ether. Its final steps require simple colorimetric readings.

With a slight change of the color standard, the test is also applicable for the determination of the amount of sulfathiazole in the blood.

The reagents required are: (1) Ether, (2) 15 per cent trichloroacetic acid, (3) 0.1 per cent solution of sodium nitrite, (4) 1 per cent solution of urea, and (5) a solution of alphadimethylnaphthylamine, containing 1 cc. in 250 cc. of 95 per cent ethyl alcohol (which should be kept in a dark bottle).

Method: Into a Luer syringe is drawn approximately 1.5 cc of venous blood. Drop by drop, 1 cc. of this blood is delivered into a round-bottomed test tube and 5 cc. of ether are added. After two minutes of vigorous shaking, the fluids separate into two layers.

Exactly 0.5 cc. of the floating layer of ethereal extract is decanted into a marked centrifuge tube. To this is added 4.5 cc. of trichloroacetic acid and the tube is shaken for 10 to 20 seconds.

Next 0.5 cc. of the sodium nitrite solution is added, and another vigorous shaking given. Now 0.5 cc. of the urea solution is added and finally 2.5 cc. of alphadimethylnaphthylamine. The tube is closed with a rubber stopper and inverted once or twice. Its white opalescence soon changes to a purplish-red.

Five minutes should be allowed for the color to develop fully and then readings may be made by comparison with prepared color standards.

These color standards may be readily prepared by using phenol red. They will last for six months. They are so calibrated that the value of sulfapyridine obtained from the sample corresponds to its true value. Five color standard tubes are used. In each of five 100 by 12 mm. test tubes are placed first the following solutions: 3.9 cc. of fifteenth molar potassium dihydrogen phosphate, 6.1 cc. of fifteenth molar secondary sodium phosphate, 0.2 cc. of normal sodium hydroxide, and varying amounts of phenol red.

The indicator itself is made up by dissolving 0.0075 Gm. of phenol red in 100 cc. of distilled water.

If this solution is added in the following amounts to the five tubes, it will give color standards indicating the following true concentrations of sulfapyridine in the blood:

PHENOL RED INDICATES SULFAPYRIDINE

0.22 cc.up to	4 mg. per cent
0.30 ccup to	7 mg. per cent
0.46 cc.up to	10 mg. per cent
0.62 ccup to	12.5 mg. per cent
0.86 ccup to	15 mg. per cent

Marshall's Test for Sulfanilamide in the Blood and Body Fluids: This test depends upon the diazotization of the sulfanilamide and coupling of the resulting diazo compound with N (1-naphthyl) ethylenediamine dihydrochloride to form a purplish-red dye which can be estimated calorimetrically.

REAGENTS

1. Solution of trichloroacetic acid containing 15 Gm. dissolved in water and diluted to 100 cc.
2. 0.1 per cent solution of sodium nitrite.
3. Aqueous solution of N (1 naphthyl) ethylenediamine dihydrochloride containing 100 mg. per 100 cc. This solution should be kept in a dark colored bottle.
4. Solution of saponin containing 0.5 Gm. per liter.
5. 4 N hydrochloric acid.
6. Solution of ammonium sulfamate containing 0.5 Gm. per 100 cc.
7. Stock solution of sulfanilamide in water containing 200 mg. per liter. A weighed quantity of crystalline sulfanilamide is dissolved in hot water and diluted to appropriate volume. This solution will keep for several months if refrigerated. From the stock solution standards for use are prepared. These may be 1, 0.5, and 0.2 mg. per cent, which are prepared by taking 5, 2.5, and 1 cc. of the stock solution plus 18 cc. of the 15 per cent solution of trichloroacetic acid and diluting to 100 cc.

Procedure for Blood: Measure 2 cc. of oxalated blood into a flask and dilute with 30 cc. of saponin solution. After one or two minutes this is precipitated with 8 cc. of the solution of

trichloroacetic acid. The free sulfanilamide is determined in the filtrate as follows: Add 1 cc. of the sodium nitrite solution to 10 cc. of the filtrate. After three minutes standing, add 1 cc. of the sulfamate solution, and after two minutes of standing, 1 cc. of the solution N (1-naphthyl) ethylenediamine dihydrochloride is added. Compare the unknown with an appropriate standard which has been treated as above. To determine the total sulfanilamide, 10 cc. of the filtrate are treated with 0.5 cc. of 4 N hydrochloric acid, heated in a boiling water bath for one hour, cooled, and the volume adjusted to 10 cc. The subsequent procedure is as above.

Procedure for Urine: Dilute the urine to contain about 1 or 2 mg per cent of sulfanilamide; 50 cc. of the diluted urine plus 5 cc. of the 4 N hydrochloric acid are diluted to 100 cc. Treat 10 cc. of this second dilution as a blood filtrate for free, and 10 cc. heated without further addition of acid for total sulfanilamide.

Comment: If blood values of 5 mg. per cent or less are expected a 1:10 dilution of blood can be used. A 1:50 or 1:100 dilution of blood is convenient when using a photoelectric colorimeter. Sulfapyridine can be determined by this method. With blood levels above 5 mg. per cent a correction of ten per cent should be added when a 1:20 blood dilution is employed. With values below 5 mg. per cent no correction is needed. When dilutions of blood of 1:50 or 1:100 are employed the recovery is quantitative.

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Part 2



Clinical Indications for Sulfonamide Therapy

ABSCESSSES

As in the case of furunculosis (*q.v.*) one must carefully evaluate the severity of the infection with the possibility of toxic reactions from the sulfonamides before starting sulfonamide therapy. In mild infections where the collection of pus is readily accessible, incision and drainage is the preferable treatment. If sulfonamide therapy is decided upon, sulfanilamide or sulfathiazole is the drug of choice. Either is given in an initial dose of 3 to 5 Gm. orally followed by 1 Gm. every four hours night and day for a period up to five or six days.



APPENDICITIS AND PERITONITIS

Sulfanilamide: The local implantation of sulfanilamide in the treatment of peritonitis and to aid the peritoneum to overcome contamination occurring at operation has become almost a standard practice. However, it is absorbed so rapidly from the peritoneal cavity that it is uncertain whether it is effective as a local medication in the same sense as in other parts of the body. The peritoneal route offers the fastest method of administering the drug to reach effective levels in the blood.

Jackson and Collier¹ report the intraperitoneal use of sulfanilamide in 62 patients for the following indications: Operations in which spreading peritonitis was encountered or areas of suppuration were entered; operations on the colon; operations on the upper gastrointestinal tract in which soiling of the peritoneum was suspected. Twenty-nine of the 62 patients were given other sulfanilamide therapy besides the intraperitoneal implantation. Only 5 of the 62 patients had evidence of post-operative intraperitoneal suppuration and two of these five received additional sulfanilamide.

Jaundice was an outstanding complication in 9 of the 29 patients who received additional sulfanilamide therapy. The authors felt that this jaundice was due to hepatic damage in all instances, for there was no hemoclysis or sepsis to account for

it. The symptom cleared rapidly after the drug had been withdrawn.

None of the nine patients who developed hepatitis received more than 5 Gm. of sulfanilamide intraperitoneally, but six of them received additional sulfanilamide on the day of operation. The interval between the operation and the appearance of the jaundice varied from 24 hours to 7 days. Because of the danger of hepatitis, the authors feel that doses of sulfanilamide locally should not exceed 5 Gm. It was pointed out that there is no evidence that local application of sulfanilamide injures the peritoneal surfaces, and it is suggested that chemotherapy offers promise of reducing scarring (adhesion formation) in the peritoneum secondary to pyogenic infection.

Mueller and Thompson² reported 268 patients operated upon for appendicitis from January, 1940, to May, 1941, at the Roosevelt Hospital without a death. These cases were divided into acute, 201; abscess, 25; and peritonitis, 44. The most severe cases, numbering 90 or 33.6 per cent, were given sulfanilamide. In 16 of these 90 cases the drug was continued by rectum or by mouth, due to the severe pathology encountered. The dose recommended is 175 mg. of sulfanilamide per kilogram of body weight, two-thirds to be applied intraperitoneally and one-third in the wound layers. An easier guide for dosage is to take eight per cent of the number of pounds of body weight, which gives the number of grams of sulfanilamide to be used in the average case in which drainage is used. In the average case without drainage, six per cent gives the proper dose. The local application produces high concentrations within the peritoneal cavity, from 75 to 100 times the level reached in the circulating blood. This seems to have a bacteriostatic or destructive effect on the bacteria.

Tashiro, *et al.*,³ report a consecutive series of cases of peritonitis in which sulfanilamide crystals were implanted intraperitoneally and the abdomen closed without drainage. There were no untoward reactions, no intraabdominal complications,

wounds healed by first intention, and the patients were discharged promptly after a generally smooth postoperative course.

Experimental studies on rabbits showed that intraperitoneal absorption of sulfanilamide was very rapid, the maximum absorption taking place in four hours, and extremely high concentration was maintained intraperitoneally until the maximum blood concentration was reached. Nonpathological changes, gross or microscopic, were discovered in the peritoneal tissues after contact with the lethal doses of the sulfanilamide crystals. Blood sulfanilamide levels rose rapidly and to the extent of 1 mg. per 100 cc. of concentration in the blood for each gram placed within the abdominal cavity. Emphasis was placed upon the value of irrigating the peritoneal cavity and sucking out all pus in order to increase the therapeutic effect of the sulfanilamide which is not particularly effective in the presence of peptone. A dose of 4 to 10 Gm. is recommended, depending upon the patient's age.

Sterilization of Sulfanilamide Powder: Amounts of 2, 4, 6, and 8 Gm. are placed in sterile test tubes, stoppered with a cork or cotton, and sterilized with dry heat at 140° C. for two hours. This causes no change in the crystalline powder. Other sulfonamides may be sterilized in the same manner.

Sulfathiazole: While sulfanilamide holds first place for local use in so many surgical conditions, probably largely because of its solubility, sulfathiazole being insoluble, the latter drug is now getting extensive use orally or intravenously (by its sodium salt) in these same diseases. Stafford⁴ reports its use in this manner in a series of 105 patients during a two-year period who had peritonitis or abscess of appendiceal origin, five patients dying and four of these being autopsied. In none was sulfathiazole used intraperitoneally. An initial dose of 4 Gm. was given to the average adult, followed at regular intervals by a sufficient amount of the drug to obtain a blood level of 6 to 8 mg. per cent. The first two doses were given intravenously; thereafter the drug was given by mouth, unless the patient was unable to retain it. A comparison of the chief

causes of death in two series of cases is shown in the following table:

TABLE 1—CHIEF CAUSES OF DEATH

<i>Causes of Death</i>	<i>Number of Deaths</i>	
	<i>From 1931-1939 (In 479 consecutive patients)</i>	<i>From 1939-1941 (In 105 consecutive patients)</i>
Direct complication of appendicitis:		
General peritonitis . . .	13	2
Pylephlebitis . . .	4	0
Septicemia . . .	1	0
Mechanical ileus . . .	7	0
Subphrenic abscess . . .	5	0
Rectovesical fistula . . .	1	0
Spontaneous rupture of untreated pelvic abscess	1	1
Extraappendiceal complications.		
Cerebral accident	1	0
Pulmonary embolism . . .	3	1
Pneumonia . . .	4	0
"Poor-risk" patients . . .	4	1
Cause of death uncertain	4	0
Total	48	5

(E. S. Stafford Surg., Gynec. and Obst.)

Stafford believes that the low incidence of deaths from generalized peritonitis was due to the effect of sulfathiazole, and in two patients who succumbed the postoperative course was prolonged far beyond the most optimistic expectations. An equally important factor in the improved results, according to the author, has been the more adequate treatment of postoperative complications. He also believes that immediate operation is the correct treatment for acute appendicitis in any stage of the disease.

Anderson⁵ reports 22 patients with advanced disease of the appendix treated with sulfathiazole as an adjunct to surgery with one death. The average duration of illness before opera-

tion was 71½ hours. Eleven of the patients had a perforated appendix, three had advanced acutely inflamed suppurative appendicitis, and one had an inflammatory abscess involving the ileocecal junction. Sulfathiazole was used intraperitoneally in 17 cases and in five of these additional sulfathiazole was given intravenously or orally. The average total dosage in this group was 14.3 Gm. There were no complications in 15 of the cases. A child aged five, who was ill 32 hours before operation, died of hyperpyrexia and convulsions; 5 Gm. of sulfathiazole were given intraperitoneally and death occurred 20 hours after the operation. In four cases sulfathiazole was used late following operation in the treatment of complications of appendicitis. Two of these cases developed a local peritonitis followed by large abdominal wall abscesses. One case developed a pelvic abscess which finally perforated into the rectum and drained spontaneously. One case developed a peritonitis later followed by pleurisy. In this group sulfathiazole was given orally and intravenously as sodium sulfathiazole.

The treatment proved that sulfathiazole is an effective adjunct to surgery in cases of severe advanced acute appendicitis and in the complications of appendicitis.

Local Irritating Effects of the Sulfonamides: Taylor,⁶ in an attempt to evaluate the irritating effects of the sulfonamides in closed wounds, implanted 1 gr. of sulfanilamide, sulfapyridine, sulfathiazole, sulfadiazine, and sulfaguanidine under the rectus sheath of dogs. All of the drugs produced inflammatory reaction, with severe edema and accumulation of inflammatory cells. Actual abscesses were produced by sulfathiazole and sulfadiazine. The author points out that such chemical trauma violates the fundamental principles of careful surgery and wound healing. Implantation of a sulfonamide powder at the site of an appendectomy also is questioned, since it cannot elevate the concentration of the drug at a distant peritoneal pus pocket above that obtainable by systemic administration, and adhesions may result from the application to the bare peritoneum. These procedures give the surgeon a false sense of

security to the detriment of sound surgical judgment. The criticism was not directed against the local or systemic administration of the sulfonamides in ulcerations or in contaminated wounds which are left open, or the systemic use of these drugs in cases of severe peritonitis.

In spite of Taylor's criticisms, however, most surgeons feel that the advantages of the local use of sulfonamides outweigh any disadvantages. At least one writer (Ferguson) feels that the insoluble sulfathiazole, while producing a local conglomeration of the drug with some peritoneal as well as a foreign body type of reaction, is preferable to sulfanilamide, because it remains in the wound longer and exerts a longer action (three to four days). Furthermore, its effectiveness seems to be greater against a wider range of organisms.

Sutton,⁷ on the other hand, reports a case illustrating the danger of intestinal obstruction from the intraperitoneal use of sulfathiazole. A boy, aged ten, had been ill for three days when seen on September 24, 1941. A gangrenous appendix with a small perforation was found at operation. The appendix was retrocecal in the iliac fossa and there was considerable purulent exudate about it. The peritoneum was injected but there were no adhesions. Three Gm. of sulfathiazole were sprinkled in the iliac fossa and on the adjacent peritoneum covering the cecum and ileum where the exudate had been abundant. A Penrose drain was inserted and 2 Gm. of sulfathiazole were sprinkled throughout the wound. The patient also was given 0.5 Gm. of sulfathiazole by mouth every four hours. Bladder irritation was noted for several days. Wound healing was retarded and not completed until the twenty-eighth day after operation. One month after discharge from the hospital the patient developed severe abdominal cramps and on December 14 signs of intestinal obstruction. Operation was performed immediately, when a loop of ileum was found bound down to the parietal peritoneum posterior to the cecum, which produced a sharp kink with obstruction. The omentum also was firmly adherent at several points to the parietal peritoneum,

the ileum, and the cecum. There were no adhesions except in the area corresponding to that sprinkled with sulfathiazole, and this was covered with a fine reddish granular tissue, which on microscopic study showed only dense connective tissue with many small blood vessels. There was no evidence of sulfathiazole crystals. The wound healed in a fine scar and the patient made an excellent convalescence in nine days.

Ample experimental and clinical evidence is available to establish the fact that the local use of sulfonamide preparations is an exceedingly valuable procedure in the prophylaxis and treatment of wounds sustained in civil life, says Herrell.⁸ Certainly, he says, the evidence now at hand is substantial enough to justify the continued local use of these compounds under civil conditions. Of the many compounds available, the choice for local use probably should rest among sulfanilamide, sulfadiazine, and sulfathiazole. Some of the difficulties that have been encountered with sulfathiazole may have been due to the rather large amounts of material used and to the fact that it has not been dispersed evenly over affected surfaces. *If finely powdered or crystalline sulfathiazole is dispersed as a thin coating rather than being "packed" in these wounds, much of the irritation and foreign body type of reaction can be avoided.* Since its antibacterial activity is polyvalent, if the mechanical problems involved in the application of sulfathiazole can be overcome, it is obviously superior to the monovalent compound sulfanilamide. Sulfadiazine may closely compare with sulfathiazole.

The "antisulfonamide" action of pus and tissue exudate may easily be overcome by frequent cleansing of infected surfaces, followed by reapplication of the powdered drug. This is essential in the early stages of infection. Other minor objections to the local use of sulfonamides, such as absorption into the general circulation, local damage to tissue, and the development of resistant strains of bacteria, are easily discountable on the basis of excellent experimental and clinical experience. Further, it is not necessary that the local agent penetrate deeply into

the tissues. The actual culture medium for bacteria is the necrotic tissue and exudate. The deeper tissues possess an adequate capacity for combating infection.

There is one field in which these compounds have without question established themselves permanently in prophylaxis and treatment; namely, in intraperitoneal infection or suppuration. Five to 10 Gm. of the sterile, powdered drug should be introduced routinely into the peritoneal cavity in the presence of suppurative disease. Evidence is accumulating that prophylactically likewise this measure is sufficiently indicated.

In selecting a drug for intraperitoneal prophylaxis the following well-defined criteria should be applied: (1) The drug should be active against a variety of microorganisms; (2) it should, if possible, stimulate the local peritoneal defense mechanism, and, at the same time, be innocuous to the peritoneum; (3) it should remain in fairly high concentration in the peritoneal space as long as possible, thus exerting prolonged bacteriostatic action.

Sulfapyridine and, to a lesser extent, sulfadiazine are definite peritoneal irritants and should not be employed for this type of therapy. Sulfanilamide meets some of the criteria postulated above. It is not a peritoneal irritant and does not depress the local peritoneal defense mechanisms. On the other hand, it remains in the peritoneal fluid for only 24 hours or even less. It is monovalent rather than polyvalent.

Sulfathiazole is polyvalent. The material does not entirely leave the peritoneal fluid for a period as long as four or five days. Concentrations in the peritoneal fluid of 400 or 500 mg per 100 cc. are present following instillation of 5 to 10 Gm. Cellular elements, particularly the mononuclear phagocytes, are markedly stimulated. There is no evidence of peritoneal irritation. Abdominal cavities opened subsequent to use of sulfathiazole have not revealed evidence of abnormal adhesions or other untoward effects. Additional oral or parenteral therapy under ordinary circumstances is not necessary.

Investigators in general have experienced significant reductions in rates of morbidity and mortality following intraperitoneal use of the sulfonamides in the presence of suppurative abdominal disease. Mortality rates for abscess and rupture of the appendix in one surgical center were more than halved in the first year of its use. Peritonitis is not commonly observed at necropsy since the introduction of intraperitoneal chemotherapy.

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ATELECTASIS

Bronchoscopy, of course, is the most valuable treatment for atelectasis once the condition has developed. Chemotherapy with the sulfonamide drugs will do nothing toward bringing about a cure of the atelectasis, but it has a distinct place in treatment and should be used almost routinely to help prevent the secondary infection which develops so commonly in the atelectatic portion of the lung. For dosage, see pages 22 and 121.



BACTEREMIA

See page 127



BLEPHARITIS

See page 265

BRONCHITIS

See pages 6, 128, and 309



BRONCHOPNEUMONIA

Although Gordon¹ states, "Sulfathiazole should be administered at the onset as in the case of lobar pneumonia," it is doubtful if the sulfonamides are useful drugs in bronchopneumonia. Sometimes sulfonamides are administered in this disease with the idea of warding off lobar pneumonia, but here again the words quoted under Respiratory Infections about the use of sulfonamides in the common cold² bear repetition.

If only about one out of every 1000 patients with colds develops pneumonia, it seems hardly fair to subject the rest of them even to the apparently slight hazards of toxicity or sensitization to drugs. Then again, of the 0.1 per cent who do develop pneumonia, the disease will not in all cases be caused by the pneumococcus, and the value of sulfonamide chemotherapy for hemolytic streptococcic or staphylococcic pneumonia is far from being proved. And it is of no value in pneumonias caused by viruses.

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BRUCELLOSIS

Davis¹ believes that brucellosis may be a primary disease of the digestive tract, with a spread to the rest of the body either through septicemia or as the result of toxins picked up in the digestive tract and circulated throughout the body. If this assumption is true, he says, an intestinal antiseptic should be the answer to our general therapeutic problem. He continues:

Such an antiseptic should not be absorbed from the digestive tract, should remain active in the presence of digestive proc-

esses, and should be nontoxic so that it could be used over a long period of time. Sulfasuxidine answers these requirements. In September of 1942 I started the use of this drug in all my cases, and the results have been very gratifying.

A case history which is very typical of chronic brucellosis is that of E. M., who came to me in May of this year. She stated that a year ago, while living in another community, she developed pains in the upper right quadrant of the abdomen. This was accompanied by pain and marked weakness in the back, which radiated down into the thigh. She had some pain in the left shoulder and in her knees. The symptoms became so severe that she was forced to give up the care of her home. She consulted a physician, who diagnosed the condition as gallbladder disease and started appropriate therapy. After six months of treatment her condition was unchanged, and she was advised to go to the hospital for x-ray study and possible surgery. The x-ray study revealed a normal gallbladder with no stones, and she was sent home with her condition unchanged. Upon moving to my community she consulted me. A physical examination was negative, except for abdominal tenderness which had shifted to the left side. A blood agglutination test was made and she was found to react in a dilution of 1 to 200. She was immediately placed on sulfasuxidine, 0.5 Gm., three times a day. One week later her abdominal pain was gone, and on the following week she stated that all of her symptoms had diminished. Since then she has taken over the care of her household and has been able to do considerable work in her garden. The blood titers have been very interesting to follow. On vaccine therapy the titer is seen to rise. On sulfasuxidine the blood titer comes down, as seen in the table on page 108 taken from records of the above case.

According to the manufacturer, sulfasuxidine remains in the digestive tract, only five per cent being absorbed. Inasmuch as this is true, one can reasonably assume that the full effects of the drug are on the digestive tract. Since symptoms, such as pain, weakness, uterine hemorrhage, and exanthemata in distant parts of the body, are readily relieved by sulfasuxidine, one is led to

TABLE 1

	1/25	1/50	1/100	1/200
1st week	4 plus	3 plus	2 plus	1 plus
2nd week	4 plus	3 plus
3rd week	4 plus	3 plus	trace	..
4th week	4 plus	3 plus		..
6th week	4 plus	1 plus	..	

the belief that the primary focus must be in the colon. Harris and others have demonstrated foci of infection in bone and in other tissues, and undoubtedly at times a septicemia will produce metastatic lesions over the body which could not be expected to respond to sulfasuxidine. Inasmuch as the active radical of sulfasuxidine is sulfathiazole, it is easy to understand how this drug can be helpful in such metastatic cases. To date I have treated 18 cases with sulfasuxidine. Ten cases have been dismissed and are apparently cured, six are much improved but still under treatment, and two cases have up to the present time shown no response to the drug. At the present time I am unable to give any explanation of the two failures; however, they are still under study.

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SEVERE BURNS

Patients dying of severe burns do so from shock or from toxemia and infection. The first thought in therapy, therefore, should be the combating of the shock. Heat is a requisite and it is a good plan to immerse the patient at once, fully clothed, in a bath of normal salt solution at 100° F. This gives the necessary heat to combat the shock and at the same time loosens clothing which has become adherent to the body. If the warm bath is impracticable, heat should be applied by wrapping the patient in warm blankets and applying hot water bottles all

about him. Morphine should be given at once hypodermically for the pain and this measure also reduces the shock.

Débridement, that is, the surgical removal so far as is possible of all burned tissue, should be superficial and confined only to tissue which is obviously loose and destroyed, and to foreign matter in the wound. Some surgeons recommend that this be done under anesthesia, but anesthesia is quite likely to augment the shock. *It is much better to use morphine narcosis.*

The severe burn has caused an escape of large quantities of plasma from the circulating blood into the injured tissue, and much of this has been lost from those surfaces no longer having a protective covering. The resulting hemoconcentration may prove fatal if not overcome promptly. Plasma should be given intravenously if available, or, if not, either dextrose solution (50 Gm. of dextrose in 1000 cc. of distilled water) or physiologic salt solution (8.5 Gm. of sodium chloride in 1000 cc. of distilled water) should be given intravenously.

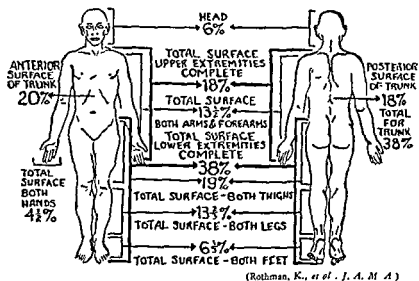
Local Treatment: The spraying of burns with a tannic acid solution has been a standard practice for some years, but of late several competing treatments have been receiving a great deal of attention. Pickrell¹ introduced one of these in 1941 and a report on this method of treatment has been made by Rothman, Tamerin, and Bullowa.²

The local treatment was application of 2.5 per cent sulfadiazine in eight per cent triethanolamine solution,* in accordance with the method of Pickrell, modified to provide rapid formation of an eschar by desiccation of the exuded serum. The method used was as follows:

On admission of the patient to the accident ward, usual methods to combat shock are promptly instituted. These are frequent plasma infusions (as much as 2500 cc.), adrenal cortex

* The 2.5 per cent solution is clear but darkens on exposure to light and consequently is stored in a dark bottle. It is almost colorless and does not stain the tissues or linen. The drug is absorbed through the early eschar, reaching its highest level in the blood stream on the second day and receding thereafter until it has disappeared from the blood stream on the sixth day. Blood stream levels range from 2 to 8 mg. per hundred cubic centimeters.

extract (1 cc. each day), and warmth. If the clothing is adherent, it is removed under morphine narcosis by soaking the patient or part involved in a tub of water at 100° F. Usually the clothing is not adherent and can be cut away. The patient is then placed on sterile sheets and with aseptic technic the wound is cleansed. The surgeons wear caps, masks, sterile gowns, and gloves during the procedure. Blisters are opened and loose shreds of epithelium and skin are removed. The area is again sponged with sterile water at 100° F. If all the dirt is not removed by this technic we use the suds of white



(Rothman, K., et al. J. A. M. A.)

Fig. 1—Berkow's method of estimating extensiveness of cutaneous lesions.

soap on cotton balls. Grease is removed with ether or benzine. The entire procedure is carried out without anesthesia, rapidly, and without pain. Green soap, gauze, and scrubbing are not used.

The 2.5 per cent sulfadiazine in eight per cent triethanolamine is sprayed on the surface of the wound every hour on the first day. After each application, the surface of the wound

is dried by fanning, or, more recently, by an electric hair dryer with warmed air. The same procedure is carried out every two hours on the second day, every three hours on the third day, and every four hours on the fourth day. A heat cradle is used to maintain the body temperature. Care should be taken to avoid any burns from this source. At all times aseptic technic is maintained. Physicians, nurses, and visitors wear caps, masks, and gowns.

A thin, pliable, and translucent eschar forms in 24 to 36 hours and after the fourth day spraying is rarely necessary. No dressings are applied at any time. Sedatives are rarely required after the eschars are formed and nursing care is minimal. Between the tenth and the twelfth day the edges of the eschar tend to curl; at this time wet dressings of the sulfadiazine triethanolamine solution are applied. As the eschar curls at its edges a potential portal of entry for bacteria forms. Wet dressings of 2.5 per cent sulfadiazine in 8 per cent triethanolamine solution are applied at this stage in order to prevent secondary infection. Sometime between the twelfth and the twenty-second day the eschar will be completely separated, and its removal may be facilitated by cutting away the loose portions. When infection occurs, purulent material is readily visible because the eschar is translucent. A window is cut in the eschar to permit drainage. Wet dressings of the sulfadiazine solution are applied over the infected area until the infection has cleared. The procedure is the same for second- and third-degree burns. The spray has been used about the face, eyes, and mucous membranes without injury. Similarly, the 2.5 per cent sulfadiazine in eight per cent triethanolamine solution is used on joints and fingers without constriction or limitation of motion. The eschar is pliable and does not crack.

In the Cocoanut Grove disaster in Boston the burn victims were not treated with tannic acid, according to Faxon and Churchill.³ The authors state that the burns were treated by a single method. There was no cleansing or débridement. (One patient only with a second-degree burn had superficial cleans-

TABLE I—OBSERVATION IN 32 CASES

Case	Age	Sex	Color	Day of Admission	Etiology	Shock on Admission	Previous Therapy	Stay in Hospital	Time in Hospital	Days Before Grafting	Area Involved	Extent of Burn	Infection and Day
1	1	♂	N	1	Fire, clothes	None	None	16	20	..	Arm, hand	12% 2d degree	None
2	33	♀	N	1	Scald, hot water	None	None	5	15	..	Face, neck, chest	15% 2d degree 3% 3d degree	None
3	24	♂	N	3	Fire, clothes	None	Ointment	15	18	..	Abdomen	10% 2d degree 3% 3d degree	Beta streptococcus, 11th
4	50	♂	W	1	Explosion	80/60	None	16	52	23	Face, hands, neck, foot, chest	15% 2d degree 5% 3d degree	None
5	8	♂	N	1	Fire, clothes	None	None	16	18	.	Abdomen, back	18% 2d degree 5% 3d degree	None
6	35	♂	N	4	Flame, benzene	None	Ointment	38	54	22	Leg, hands	4% 2d degree 14% 3d degree	Staphylococcus aureus, 11th
7	3	♀	W	1	Radiator	70/50	Oil	20	28	Ready on 24th; signed out	Arm, thigh, leg	12% 2d degree 8% 3d degree	None
8	45	♂	N	2	Scald, hot water	Mild Shock	None	20	24		Abdomen	11% 2d degree 4% 3d degree	None
9	49	♂	N	4	Scald, hot water	None	Ointment	17	24		Chest, shoulder	12% 2d degree	Staphylococcus aureus, 12th
10	57	♂	N	1	Fire, kerosene	None	None	11	12	.	Leg	14% 2d degree	None
11	3	♀	N	1	Hot stove	None	None	12	14	.	Buttock, abdomen	14% 2d degree	None
12	11 mo.	♀	N	1	Scald, water	None	None	8	9	.	Chest, abdomen, face	10% 2d degree 3% 1st degree	None
13	5	♂	N	1	Hot oil	None	None	10	12		Back	12% 2d degree	None
14	2	♀	N	2	Hot stove	None	None	22	29	..	Abdomen, thigh	15% 2d degree 4% 3d degree	Beta streptococcus, 12th
15	21	♀	N	1	Flame, clothes, scald	84/58	None	24	28	.	Legs, neck	11% 2d degree 3% 3d degree	None
16	3	♂	W	1	Scald, coffee	None	None	22	26		Neck, arm, chest, thigh	20% 2d degree 4% 3d degree	None

TABLE 1—OBSERVATION IN 32 CASES—Continued

Care	Age	Sex	Color	Day of Admission	Etiology	Shock on Admission	Previous Therapy	Stay in Bed	Time in Hospital	Days Before Grafting	Area Involved	Extent of Burn	Infection and Day
17	23	♀	N	1	Fire, clothes	88/62	None	25	27		Abdomen, leg	17% 2d degree 4% 3d degree	None
18	18 mo	♂	N	3	Scald, tea	None	Ointment	10	14		Chest	16% 2d degree	None
19	4	♀	N	1	Scald, water	None	None	20	26		Abdomen, chest, thigh	19% 2d degree 5% 3d degree	None
20	22	♂	N	1	Scald, water	None	None	19	21		Face, neck, chest, thigh	16% 2d degree 3% 3d degree	None
21	33	♂	N	2	Scald, water	None	Ointment	11	13		Leg	11% 2d degree	Staphylococcus aureus, 11th
22	42	♀	N	1	Fire, clothes	40/20	None	Died in 28 hours			Arm, chest	22% 3d degree 5% 2d degree	Staph. aureus, Beta streptococcus, 10th
23	32	♂	W	1	Fire, clothes	80/60	None	60	78	38	Chest, abdomen, leg	30% 3d degree 8% 2d degree	Beta streptococcus, 14th
24	32	♂	N	3	Fire, clothes	None	Ointment	54	60	34	Legs	12% 3d degree	None
25	8 mo	♂	W	1	Explosion	60/40	None	28	68	30	Scalp, hands	18% 3d degree	None
26	5	♀	N	1	Fire, clothes	60/38	None	40	84	44	Neck, face, chest, arm	30% 3d degree 8% 2d degree	None
27	28	♀	N	1	Fire, clothes	88/64	None	38	74	44	Arm, back, neck	16% 3d degree 18% 2d degree	Alpha streptococcus, 10th
28	18 mo	♀	N	1	Hot cereal	40/20	None	22	27	..	Abdomen, chest	22% 2d degree	None
29	30	♀	N	1	Scald, water	None	None	19	20	.	Face, abdomen, back	22% 2d degree	None
30	23	♀	N	2	Fire, clothes	64/30	None	In hospital condition good			Abdomen, chest, thigh	40% 3d degree 8% 2d degree	Staphylococcus aureus, 12th
31	29	♀	W	1	Fire	30/0	None	Died in 40 hours			Abdomen, chest, arm	40% 3d degree	None
32	30	♀	N	1	Hair drier	60/20	None	In hospital condition good			Scalp, face, abdomen, chest, arm	45% 3d degree	None

(Rothman, K., Tamerin, J., and Bellowa, J. G.: *J. A. M. A.*)

ing with soap and water to remove carbon from the hands and the face.)

The burned surfaces were covered with fine mesh gauze impregnated with boric ointment. Gauze, sterile mechanics' waste, and cotton roller were utilized to form a bulky dressing. This was compressed snugly with elastic bandage to form a pressure dressing. Splints of folded newspaper, as suggested by the Red Cross, were used for the forearms and hands.

The eyes were examined by a resident from the Massachusetts Eye and Ear Infirmary. Seven patients had lesions involving the lower half of the cornea; five per cent sulfathiazole ointment was applied and atropine drops were instilled. All eyes were reexamined at 10 A. M. and the corneal lesions evaluated with fluorescein. The sulfathiazole ointment was reapplied.

Two Gm. of sulfadiazine were given intravenously at 2 A. M. to all patients, including those without surface burns. This was repeated at 10 A. M. Thereafter those able to take the drug by mouth received 1 Gm. every six hours. Patients unable to take the drug by mouth received further intravenous medication at 12 noon, at 9 P. M., and every 12 hours thereafter. Blood levels of 5 to 10 mg. per 100 cc. have been established, the average being 7 mg.

Another form of local treatment is the application of one per cent aqueous solution of gentian violet. No preliminary cleansing of the burned area is done unless it is covered with oils and grease. The patient is maintained in a comfortably warm cradle and the gentian violet solution is sprayed on every two hours in the beginning, while the sterile eschar is forming and the wet oozing areas are becoming dry and tough. Blebs are then opened and the spraying continued at four- to six-hour intervals until healing is complete.

Andrus, Nickel, and Schmelkes⁴ report the use of preformed hydrated chemotherapeutic membranes (eschars) in the treatment of second-degree burns in ten patients. These membranes were made of ten per cent sulfanilamide with a buffer, with or without azochloramide. Excessive oozing may threaten

to destroy the membrane after application and a second and a third application can be made over the first. By mounting the sheets on gauze they can be made large enough to encircle the torso of an adult.

The authors report that the longest time required for complete healing was 21 days, and this was in a case in which an extensive burn about the head involved all the hair and the eyebrows.

The technic used was as follows: The burn was first débrided and thoroughly cleansed with saline, boric acid, or azochloramid solution. All dead skin was removed and the preformed membrane was applied directly to the raw oozing surface. A dry sterile dressing was placed over the membrane and held by a plain gauze bandage. Given a large number of burns (on board ship, for instance) the membrane can be applied quickly and easily by any one trained in first aid and can be held in position by the dry dressing. If its removal is necessary, it is moistened with sterile water or saline solution.

Since submitting their paper the authors have treated ten additional patients who had severe second-degree burns; their average healing time was nine days. The burn of one patient involved 55 and of one patient 35 per cent of the surface of the body. Healing in both was complete in 12 days.

In conclusion, it would seem wise, no matter what form of local treatment is used for severe burns, to give sulfathiazole by mouth if possible or intravenously if it is not. It is quite probable that the good results obtained following the Cocoanut Grove disaster were due largely to this measure.

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CARBUNCLE

Sulfathiazole is the drug of choice for carbuncles. The initial dose is 3 to 4 Gm. orally, followed by 1 Gm. every six hours night and day. The full effect of the drug will be achieved within four to five days, when it should be discontinued.



CELLULITIS

See page 167



CEREBROSPINAL FEVER

See Meningitis, page 132



CHANCROID

Prophylaxis: In the section on Gonorrhea there is a report which shows that under sulfathiazole prophylaxis chancroidal as well as gonococcal infections virtually disappeared. The same is not true of the older types of prophylaxis, as is pointed out by Greenwald.¹

Mechanical as well as chemical prophylaxis following sexual intercourse is frequently urged on each soldier. He receives many lectures by medical and line officers and is exposed to training films concerning sex hygiene at frequent intervals. The chemical prophylaxis which is recommended by the Army consists of: (1) Initial thorough cleansing of the genitalia with green soap; (2) thorough washing of the parts with 1:1000 mercury bichloride; (3) urethral injection of five per cent mild protein silver, and (4) thorough application of ointment of mild mercurous chloride to the parts.

With this method of prophylaxis we find very few failures with respect to syphilitic or gonorrheal infections. However, chancroidal infections are apparently more resistant, and we were much surprised on reviewing our prophylactic failures

to observe that a disproportionately large number of these had developed chancroid. Whether this disproportion reflects the more chemoresistance of the organism as compared with the gonococcus and *Treponema*, whether the prophylaxis is not being adequately applied to the "danger zones" of Ducrey infection, or whether this is a chance circumstance in a relatively small number of cases we are not prepared to state. If this experience is generally corroborated throughout the Army, further investigation is indicated.

In our series, 38 per cent of the patients had had a chemical prophylaxis, 29 per cent within one hour or less from the time of exposure. This experience is contrary to the experience of most reports. Thomas feels that soap and water thoroughly applied within one hour of the contact is effective. This rate of failure compares very unfavorably to results in gonorrhea and syphilis, in which it comprises no more than 0.8 per cent.

Treatment: Until the advent of the sulfonamides the treatment of chancroidal infection was symptomatic rather than specific. During the World War treatment consisted of good local hygiene, under which many chancroids healed spontaneously. However, in progressive cases or very early infections, the thermocautery or the chemical cautery was used with varied success as *definitive or abortive treatment*. Frequently there was extreme tissue destruction and scarring. In 1918 the average noneffective days or time lost from duty represented 24.9 days.

Since 1918 many therapeutic measures have been recommended, running the gamut from complex mixtures to surgical excision. All of these have been replaced by the sulfonamide drugs, surgery being indicated only when drainage and exposure of the lesion are extremely poor because of phimosis or paraphimosis. *The prognosis has undergone a great change in recent years, since sulfonamides have been found useful.*

*Prerequisite to the intelligent treatment of penile lesions is the recognition of the frequency of mixed infections. It is our practice to search for *Treponema pallidum* repeatedly in penile*

lesions subsequent to the positive diagnosis of Ducrey infection, withholding all local therapy until a minimum of four consecutive dark field examinations have been found negative. During this period treatment with sulfathiazole is initiated by mouth. In our experience, often necrotic and heavily secondarily infected lesions become clean and *Treponema* is then more easily found in the expressed serum.

In this series we have found a chancroidal lesion coincident with syphilis in ten instances. These cases presented, however, no problem in therapy, for no adverse reaction marked the simultaneous use of sulfathiazole and daily full doses of mapharsen as used in our clinic in the treatment of primary syphilis.

Once the diagnosis of Ducrey infection is made, our routine consists in the administration of sulfathiazole in 4 Gm. (60 grains) daily doses, the initial dose being 2 Gm. (30 grains). The drug is continued in these doses for a minimum of seven days with careful observation for toxic phenomena. In no case in this series was there indication for withdrawal of the drug because of toxicity.

After a minimum of four negative dark field examinations, during which local application of saline dressings was used, the lesions were treated twice daily with soaks of 1:8000 potassium permanganate, followed by the application of sulfanilamide powder.

Under this regimen all patients rapidly improved, with an average of 7.6 days of time lost from duty. No patient was discharged from the hospital until the lesions had completely epithelized.

Ten per cent of our cases were admitted with fluctuant buboes and surgical intervention was necessary in all of these, since treatment by sulfathiazole alleviated none. In three cases it was noted that on admission the nodes were discrete, and in spite of favorable response of the ulceration to treatment the nodes went on to suppuration and had to be incised and drained.

There were six recurrences in this series, four of which had received less than seven days of treatment. One of these patients had received only local treatment for five days on his primary admission. Another had a mixed infection with primary syphilis. One case listed as a recurrence was probably a reinfection, since there was a time lapse of 92 days between his first and his second admission. On readmission all of these responded well to combined local and systemic therapy as outlined.

It is customary in our clinic to follow all cases of genito-infectious disease not diagnosed as syphilis by weekly serologic tests for syphilis for one month, and monthly Kahn tests for three months thereafter. However, since this post is a training center, many of the patients are transferred to other stations and field organizations. About 32 per cent of our patients were thus lost. The remaining 68 per cent have remained consistently seronegative except for two, who within four weeks returned with a positive blood test and were subsequently treated for early syphilis. Of these two patients, one had had a negative smear and negative skin test, but was repeatedly negative on dark field examination and clinically was considered to have an early chancroidal ulcer. The second patient gave negative smear and positive skin tests and also healed rapidly with sulfathiazole therapy. The diagnosis of chancroid in these two cases is open to question, despite the fact that the lesions healed without antisyphilitic treatment.

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SULFONAMIDE THERAPY IN DISEASES OF CHILDREN

Nowhere are the results of sulfonamide therapy more striking than in the treatment of diseases of children. Some of the forms of meningitis, as the most outstanding example, formerly had a mortality of almost 100 per cent. Now, with adequate sulfonamide therapy, recoveries are becoming common.

TABLE 1—DOSAGE OF SULFONAMIDES FOR INFANTS AND CHILDREN

<i>Drug</i>	<i>Disease</i>	<i>Route</i>	<i>Initial Dose</i>	<i>Subsequent Doses</i>	<i>Duration of Treatment (except as foot effects force earlier discontinuance)</i>
Sulfanilamide	Beta-hemolytic streptococic infections	Oral. May pulverize tablet and give with food, drink	0.1 Gm. per kg. (1 Gm. per 22 lb.) (0.7 grain per lb.).	1/6 initial dose q. 4 h. day and night. May give equal quantity of soda bicarbonate.	Continue until temperature is normal for 72 hours.
Sulfanilamide	Severe streptococic infection or meningococic infection.	Oral.	0.15 Gm. per kg. (1 grain per lb.)	1/6 initial dose q. 4 h. day and night	Continue until temperature is normal, then reduce dose by one-third and continue until temperature is normal for 72 hours.
Sulfapyridine	Pneumococic pneumonia.	Oral	0.06 Gm. per lb. for patients under 40 lb (18 kg.). Slightly less per lb. for larger children 2.4 Gm. for 40 lb. 2.6 Gm. for 50 lb. Not over 3 Gm. for 60 lb.	1/4 initial dose q. 6 h. day and night (May give 1/6 initial dose q. 4 h. if preferred.)	Continue until temperature is normal, then reduce dose by one-third and continue until temperature is normal for 72 hours.
Sulfathiazole	Pneumococic pneumonia or moderately severe staphylococic infections	Oral.	0.15 Gm. per kg. up to 25 kg., 1/2, 1 Gm. for each 15 lb. up to 60 lb. body weight.	1/6 initial dose q. 4 h. day and night. Adequate fluids. May alkalize urine.	Continue until temperature is normal for 36 hours
Sulfathiazole	Severe staphylococic infections.	Oral.	0.2 Gm. per kg. up to 20 kg. of weight (1 Gm. for each 11 lb. up to 44 lb.).	1/6 initial dose q. 4 h. day and night. Large quantity of fluid. Alkalize urine.	Continue until temperature is normal for 48 hours. Then 1/9 initial dose q. 4 h. for 14 days. Then 1/18 initial dose q. 4 h. for 14 days more. Frequent leukocyte counts especially indicated after prolonged therapy.
Sulfadiazine	Pneumonia.	Oral.	0.1 Gm. per kg. (1 Gm. for each 22 lb.)	1/4 initial dose q. 6 h. Adequate fluids. May alkalize urine	Continue until temperature is normal for 48 hours.
Sulfadiazine.	Severe pneumococic, streptococic, staphylococic or meningococic infections	Oral.	0.15 Gm. per kg. (1 Gm. for each 15 lb.).	1/4 initial dose q. 6 h. or 1/6 l. d. q. 4 h. Large quantity of fluid. Alkalize urine.	Continue drug until temperature is normal for 48 hours. Then reduce dose by 1/3 and continue 5 days longer.

Dosage

Infants and children as a rule tolerate the sulfonamides better than do adults and require larger doses per pound of body weight. Solomon¹ gives the following information on dosage:

The objective of dosage is a therapeutically adequate concentration of free drug in the blood. This concentration, however, may be affected by several factors: Individual variations in the rapidity of absorption and excretion of the drug; the fluid intake; state of hydration of the body tissues; the degree of acetylation, and the urinary output. Unless conditions indicate otherwise, the fluid intake should not exceed 3000 cc. in 24 hours, and an attempt should be made to maintain a 24-hour output of urine of not less than 1500 cc.

The dosage suggested must be modified in some cases where optimum blood concentration is not being achieved. The amount of drug given depends primarily on the weight of the patient and the level of concentration of the drug desired in the blood.

Sulfanilamide: *Peroral:* Ten to 15 mg. per cent. free sulfanilamide in the blood desired: Give 1 to 1½ grains per pound of body weight for the first 24 hours. Initial dose should be one-third of the total 24-hour dose and the remainder should be divided into five equal doses given every four hours.

Example: Patient weighs 50 pounds. Initial dose, 25 grains (five five-grain tablets); then 10 grains (two five-grain) tablets every four hours. Continue with this dose until clinical improvement occurs and the temperature drops to normal. Then decrease the dose—say, 50 per cent—and decrease the frequency—say, to three or four times a day.

Hypodermoclysis: Subcutaneous route is preferable and drug is given in one per cent solution in physiologic saline solution, Hartmann's solution, or sixth molar sodium lactate solution. Solutions must be prepared fresh for each 24-hour period.

Technic: Solution should be heated and allowed to boil for a few minutes; it is then allowed to cool below the boiling

point. Crystalline sulfanilamide powder is then added and the solution allowed to cool to body temperature. One-half the calculated 24-hour dose is administered by hypodermoclysis, and one-quarter the 24-hour dose repeated at eight-hour intervals.

Example: Patient weighs 50 pounds, and is to receive $11\frac{1}{2}$ grains per pound of body weight in 24 hours (5 Gm. or 75 grains). Five Gm. must be dissolved in 500 cc. of physiologic saline or other desired solution. Then 250 cc. of this solution is given as the first dose and 125 cc. repeated at eight-hour intervals.

Sulfapyridine: Peroral: Sulfapyridine is less soluble than sulfanilamide and there are marked individual variations in the degree and rate of absorption of the drug. It is therefore more difficult to state a rigid dosage. One must be guided by the determination of the blood concentration and clinical response. Five to 10 mg. per cent sulfapyridine in the blood desired: Give 1 grain per pound of body weight in first 24 hours. The total 24-hour dose should not exceed 100 grains for children over 12 years of age, nor 80 grains for children under 12 years of age. The initial dose should be one-third the calculated 24-hour dose, and the remainder is divided into five equal doses, each given every four hours. After the temperature has remained normal for 24 to 36 hours, the 24-hour dose can be decreased to 50 to 75 per cent of the first 24-hour dose.

Hypodermoclysis: The alkalinity of this solution apparently does not irritate the tissues. Physiologic salt solution is used as the vehicle and the drug is dissolved to a strength ranging from 0.3 to 0.7 per cent. Thus, if the calculated dose is 5 Gm., it should be dissolved in 1000 cc. of physiologic saline solution to make a 0.5 per cent strength. For the technic of administration see Technic for hypodermoclysis under sulfanilamide. The rate of flow should be 200 to 250 cc. per hour. To obtain an adequate blood concentration quickly, sodium sulfapyridine

(2 to 3 Gm.) should be given intravenously, then followed by hypodermoclysis of sulfapyridine.

Intravenous: Intravenous administration is indicated in cases of severe pneumococcic infection in order to get a rapid optimal blood concentration. It is also used when vomiting or poor absorption from the small intestine makes it difficult to achieve a good blood concentration.

Sodium sulfapyridine monohydrate is a white crystalline powder, soluble in water at room temperature to the extent of 54 Gm. per 100 cc. of solution. Solutions of 0.2 Gm. to 40 Gm. in 100 cc. are strongly alkaline, having a pH from 10 to 11. If given intramuscularly or intrathecally, necrosis of tissue may take place. When they are injected intravenously, care should be exercised to prevent any escape of fluid outside the vein. It is marketed in ampules (Abbott) of 1, 4, and 6 Gm., and in bottles (Lederle) of 5 Gm. The drug is administered in five per cent solution in sterile physiologic saline solution or distilled water. One may give a less concentrated solution in a larger volume of physiologic saline solution. *Caution!* This solution should not be given with a blood transfusion or infusion of dextrose. Also, if this solution is given more than once or twice, venous thromboses may occur.

Five to 8 mg. per cent free sulfapyridine in blood desired: The initial dose is 0.03 Gm. ($\frac{1}{2}$ grain) per pound of body weight.

Example: Patient weighing 60 pounds should get 30 grains or 2 Gm. This dose should be weighed out and dissolved in 40 cc. of sterile distilled water, making a five per cent solution. The rate of flow should be 5 cc. per minute.

Maintenance Dose: Perioral therapy should be started as soon as possible. If intravenous therapy must be continued a maintenance dose of 0.015 Gm. ($\frac{1}{4}$ grain) per pound of body weight should be given in five per cent solution of sterile distilled water every six to eight hours.

Rectal: Sodium sulfapyridine has been used rectally. It is given in two per cent solution as a retention enema. Initial

dose of this solution is 4 cc. per kg. of body weight; then 2 cc. per kg. of body weight is given every four hours.

Example: Patient weighs 55 pounds. Divide the pounds by 2.2 to change to kilograms—hence he weighs 25 kg. Allowing 4 cc. per kg., the initial dose should be 100 cc. of a two per cent solution (this amounts to 2 Gm. of the drug). Then, allowing 2 cc. per kg., 50 cc. of a two per cent solution should be given every four hours.

Intrathecal: Most authorities object to this method of administration. Neal, however, has made the claim that a two per cent solution does not appear to irritate the meninges.

Sulfathizole: Dosage cannot be determined with as much accuracy as in the case of sulfanilamide, because of individual variations of absorption and rapid excretion.

Peroral: In order to attain adequate blood concentration, it is often necessary to give one and one-half times the dose of sulfanilamide or sulfapyridine, or the regular dose at more frequent intervals.

Ten mg. per cent free sulfathiazole in blood desired: Give $1\frac{1}{2}$ grains per pound of body weight in first 24 hours. The initial dose is one-third of the calculated 24-hour dose, and the remainder is divided into five equal doses, each given every four hours. After the temperature has remained normal for 24 to 36 hours, the 24-hour dose can be decreased to 50 to 75 percent of the first 24-hour dose.

Sodium sulfathiazole has also been given by mouth—1 Gm. to get an adequate blood concentration more quickly. The alkalinity of the preparation does not irritate the gastrointestinal tract enough to preclude its use.

Hypodermoclysis: The same procedure is followed as used with sodium sulfapyridine (*q.v.*). The solution of sodium sulfathiazole should be between 0.3 and 0.7 per cent in strength and the rate of flow 250 to 300 cc. per hour.

Intravenous: Sodium sulfathiazole sesquihydrate (Squibb) is available in 5 to 50 Gm. bottles. Concentrations up to five per cent are used, but caution must be exercised against tissue

irritation because of the alkalinity of these solutions. Indications for intravenous administration and procedure are the same as those described for sodium sulfapyridine (*q. v.*). Dosage should be modified, however, to allow one and one-half times as much sulfathiazole. After adequate blood concentration is reached the drug can be continued by hypodermoclysis.

Rectal: Sulfathiazole is not absorbed very well from the rectum.

Intrathecal: It is questionable whether sulfathiazole or sodium sulfathiazole should be administered intrathecally, except possibly in cases of staphylococcus meningitis.

Sulfadiazine: Peroral: Dosage is the same as that of sulfapyridine and sulfathiazole, but higher blood concentrations are attained and the doses of sulfadiazine will have to be reduced as the concentration rises after a few days. Relatively smaller doses can be given at longer intervals because the drug is excreted more slowly; the blood concentration is thereby maintained for a longer time.

The dosage should be increased 50 per cent in cases of pneumococcic and influenzal meningitis.

TABLE 2—SULFADIAZINE FOR OLDER CHILDREN

<i>Blood Concentration</i>	<i>Initial Dose</i>	<i>Maintenance Dose</i>
10 to 15 mg. per cent	4 Gm. (60 grains)	1 Gm. (15 grains) q 4 h.
5 to 10 mg. per cent	2 to 3 Gm. (30 to 45 grains)	1 Gm. (15 grains) q 6 h.
3 to 5 mg. per cent	1 to 1.5 Gm. (15 to 23 grains)	0.5 Gm. (7½ grains) q 6 h.

TABLE 3—SULFADIAZINE FOR INFANTS AND SMALLER CHILDREN

<i>Age</i>	<i>Initial Dose</i>	<i>Maintenance Dose</i>
Under 6 months	0.5 Gm.	0.25 Gm. q 6 h.
6 months to 3 years	1 Gm.	0.5 Gm. q 6 h.
3 years to 10 years	2 Gm.	1 Gm. q 6 h.

Intravenous: Sodium sulfadiazine is administered intravenously in five per cent strength, the diluent being physiologic saline solution or distilled water. Caution must be exercised in injecting the solution because of its alkalinity. The dosage is 0.3 Gm. ($1\frac{1}{2}$ grain) per pound of body weight. This will ordinarily produce a blood concentration of about 10 mg. per cent. If the peroral method cannot be used, the same dose can be repeated intravenously every 8 to 12 hours. Blood levels should be determined once or even twice daily.

Hypodermoclysis: The drug should be administered in 0.3 to 0.8 per cent physiologic saline solution. The rate of flow should be 250 to 300 cc. per hour. Blood levels must be determined every 12 hours to control the dosage. In severe infections an initial dose of sodium sulfadiazine should be administered intravenously and then followed by hypodermoclysis every 8 to 12 hours.

Rectal and Intrathecal Routes: These are not recommended.

Sulfaguanidine: Sulfanilamide should not be used simultaneously with sulfaguanidine either locally or by other routes.

Peroral: Acute Bacillary Dysentery: Initial dose, 0.1 Gm. ($1\frac{1}{2}$ grains) per kg. of body weight; then 0.06 Gm. (1 grain) per kg. every four hours, day and night, until the stools number five or less a day; then 0.1 Gm. ($1\frac{1}{2}$ grains) per kg. every eight hours for at least three days. The drug should not be given longer than 14 days.

Prophylactic Use in Abdominal Surgery: This use of sulfaguanidine has special use in cases of resection of the colon where the danger of fecal contamination of the abdominal cavity exists. The dosage is 0.06 Gm. (1 grain) per kg. of body weight every eight hours for five to seven days before operation. If the patient can take the drug orally after operation a similar dose is given for seven days, so that the total period of administration does not exceed 14 days. If the drug must be continued beyond 14 days, repeated blood counts should be made to exclude neutropenia.

Elimination of Sulfonamides in Breast Milk: While sulfonamide is eliminated in breast milk, its amount is quite small, averaging only about 0.3 to 2 per cent of the total amount taken by the mother.. A daily oral dose of 3 Gm. will bring about the elimination in the milk of between 0.5 and 1.5 mg. per 100 cc.; a daily dose of 6 Gm. will give an elimination in the breast milk of about 1 to 2 mg. The mother's corresponding blood level is generally two or three times higher than that in the milk. A nursing infant will ingest during the course of a day only about 4 mg. of the sulfonamide, and this amount is too small to exert a therapeutic effect on the infant.

Repeated Administration of Sulfonamides to Children

Fink and Wilson¹⁸ report on the incidence of acquired sensitivity to sulfadiazine and sulfathiazole in 177 children, who had received a sulfonamide drug in two or more courses and who had had no reaction during the first course. Three febrile reactions developed in the 86 patients who were given sulfathiazole, and four febrile reactions in the 91 given sulfadiazine. It is suggested that these reactions could have been toxic reactions rather than a manifestation of sensitivity. Two of the seven children with initial reactions were given a second and a third course of the drug without reaction. Three of five children who had had reactions during a first course developed an "immediate" type of febrile reaction during a second course of sulfonamide. These studies show that sensitization to sulfathiazole or sulfadiazine is not common or frequent in children, but that one reaction greatly increases the probability of future reactions. The authors believe that if a child develops toxic reactions during the first administration of a sulfonamide, subsequent administration of the drug should be cautious and under close observation.

Bacteremia

Hemolytic streptococcic bacteremia frequently occurs as a complication or extension of severe infections by these organisms in other parts of the body, and adequate sulfonamide therapy

with sulfadiazine, sulfanilamide, sulfapyridine, or sulfathiazole² is indicated. Herrell and Brown³ state: "It is conservative, we think, to estimate that this form (adequate sulfonamide) of therapy for septicemia has almost doubled the rate of recovery." Berry⁴ believes with others that energetic chemotherapy in most cases will bring about prompt sterilization of the blood stream and improvement in the lesion responsible for the septicemia.

Whatever sulfonamide is used it will have no effect on an existing toxemia and antitoxin therapy should be considered for this phase of the disease.

The causes of failure of sulfonamide therapy are inadequate concentration in the blood of the drug, the presence of metastatic foci, and organisms which are refractory to the drug where the patient fails to establish an immune mechanism.

Other forms of therapy should not be neglected, such as blood transfusions and prompt surgical intervention.

Bronchitis

Capillary bronchitis and acute bronchiolitis are very common infections in young children and possibly have a variety of causes. Some observers feel that they are primarily virus infections with bacteria as secondary invaders. As a consequence, the results from chemotherapy are not clear-cut. Risser⁵ and Hubble and Osborn⁶ have reported the successful use of sulfapyridine in these conditions. Sulfadiazine might be used instead because of its usefulness against a variety of organisms.

Diarrhea

Halpern and Cunningham⁷ made a study of the effectiveness of sulfathiazole and sulfaguanidine in the treatment of acute diarrhea. Sulfathiazole was used in 23 children in an initial dose of $\frac{1}{2}$ grain per pound, followed by 1 grain per pound, divided into six equal doses. Sodium sulfathiazole was given intravenously to patients who were critically ill. The drug was discontinued 24 hours after the stools became normal. Blood levels ranged from a trace to 13 mg. per cent with an average

of 2.6 mg. per cent. No toxic effects from the drug were noted. Fever and toxicity subsided within 24 to 36 hours. In an average of five days the stools became normal in number and of good consistency.

Sulfaguanidine was given to 13 children, five receiving doses equivalent to those of sulfathiazole and the remainder receiving $\frac{3}{4}$ grain per pound initially, followed by $2\frac{1}{2}$ grains per pound, in six equal doses during the 24 hours. No unfavorable reactions were noted. Blood levels ranged from a trace to 2.25 mg. per cent, averaging slightly more than a trace. The clinical course was similar to that of the children treated with sulfathiazole. Stools became normal in an average of 5.4 days.

As a control, 11 children received no specific therapy. Their stools became normal in 12.5 days, but fever and toxicity persisted for many days and there was a prolonged convalescence.

Tudor⁸ made a similar study to compare the efficiency of sulfathiazole and sulfaguanidine in the treatment of infantile diarrhea, treating 16 patients with sulfathiazole and 15 with sulfaguanidine from the day of admission to the hospital to the fourth or fifth day after their diarrhea and other symptoms had ceased. Dosages of sulfathiazole for infants under one year of age were 1 Gm. on admission and 0.25 Gm. every four hours thereafter; of sulfaguanidine, 2 Gm. on admission and 0.5 Gm. every four hours thereafter. The dosages of each of these drugs were doubled for infants over the age of one year. The only toxic reaction noted was prolonged fever in two patients.

Of the 31 children, 16 had clinical bacillary dysentery and 15 had parenteral diarrhea. No pathogenic bacteria were isolated from any of the stools, which were cultured daily for three days after admission. Except for three patients, who did not improve on sulfaguanidine, the two drugs were equally effective in both the dysentery and the parenteral diarrhea cases.

The author's impression that sulfonamides were beneficial in checking the diarrhea in one case of typhoid fever and in three cases of paratyphoid A is at variance with the report of Hall,⁹ who noted no change in the course of five patients with typhoid

fever and of one with salmonella gastroenteritis after the administration of sulfaguanidine.

See also section on *Succinylsulfathiazole*, page 36.

Diphtheria

Under no circumstances should sulfonamide therapy be used in diphtheria. It has become a common practice to administer one of the sulfonamides to every patient with a sore throat, and when this turns out to be diphtheria there often follow disastrous complications, particularly neuritis or myocarditis, when serum is omitted or given late. It cannot be emphasized too strongly that the sulfonamides have no effect on the toxin of diphtheria. Every sore throat in children should be cultured for the possible presence of diphtheria bacillae. Even when culture shows the absence of diphtheria bacillae and that the sore throat probably is a tonsillitis, sulfonamide therapy is not indicated. See *Tonsillitis*, page 153.

Empyema

Empyema responds to treatment with sulfanilamide, sulfapyridine, or sulfathiazole, the latter two drugs being preferable. While the use of sulfonamides does not materially lessen the need for surgical intervention, they often shorten the duration of the disease and of the postoperative course and prevent the spread of the infection. Leahy,¹⁰ however, believes that it is possible to cure certain cases of hemolytic streptococcus empyema without drainage and to shorten the convalescence when they are drained. See also page 196.

Subacute Bacterial Endocarditis

The consensus at the present time is that little is to be gained from sulfonamide therapy alone in subacute bacterial endocarditis, other than a temporary improvement in the patient's condition and the sterilization of the blood, although Dick¹¹ has reported a case with the following summary: "In a case of sub-

acute bacterial endocarditis recovery from active bacterial infection followed the intravenous injection of 40 Gm. of sodium sulfadiazine. Somewhat alarming but transient renal damage occurred. There was no evidence of permanent injury to the kidneys."

Recent reports of the combined use of heparin and chemotherapy have not shown that this therapy has had any advantage over chemotherapy alone.

Sulfonamides and fever therapy, according to Lichtman and Bierman,¹² have given some of the best results of any treatment so far. Sulfanilamide or sulfapyridine is given in sufficient dosage to produce a blood concentration of about 10 mg. per cent. The drug is started before the fever therapy and continued throughout its course. The fever is induced by means of a hypertherm and body temperature is maintained between 40° and 40.5° C. (104° and 105° F.) for five hours, the treatments being given every three to five days until there is definite evidence of improvement. A nurse must be in constant attendance during a treatment to take the pulse and respiration every 15 minutes. The patients should drink about 2000 cc. of iced 0.6 per cent saline solution during the five hours of treatment. Any sign of impending cardiovascular crises is a signal to stop treatment immediately.

Solomon¹³ describes the use of sulfonamides combined with intravenous typhoid-paratyphoid vaccine. A sufficient dosage of the sulfonamide is administered to give a blood level of about 10 mg. per cent, and the drug is continued while alternate daily intravenous injections of typhoid-paratyphoid vaccine are given. The initial dose of 0.01 to 0.1 cc. is gradually increased at each injection. Solomon believes that the foreign protein shock action of this method of treatment enhances the chemotherapy to a *greater extent than is achieved through artificial fever therapy.* At least six sessions of treatment over seven to ten days should be given. If leukopenia develops the fever therapy should be discontinued until the leukocyte count returns to normal.

Erysipelas

Prior to the advent of the sulfonamides the mortality from erysipelas in infants and children ranged from 30 to 50 per cent. This has dropped with chemotherapy to the neighborhood of five per cent. Sulfanilamide has been the drug most used, but sulfapyridine and sulfathiazole also have given favorable results. Feinsten *et al.*¹⁴ showed sulfadiazine to be effective against experimental infections due to hemolytic streptococci, and the readiness with which blood concentrations can be obtained and its relatively low toxicity would seem to indicate that it is a favorable alternative chemotherapeutic agent. This has been borne out by Finland, Strauss, and Peterson,¹⁵ who reported sulfadiazine highly effective in erysipelas. Also see page 205.

Gonococcal Infections

Ophthalmia: Sulfapyridine and sulfathiazole, given orally, are of great value in the treatment of gonococcal ophthalmia. Lewis¹⁶ reports in 22 cases treated with sulfapyridine a reduction of the duration of treatment to an average of 2.57 days and in eight cases receiving sulfathiazole to an average of four days.

Vulvovaginitis: Cohn, Steer, and Adler¹⁷ report that "apparently 68 per cent of the cases underwent a so-called 'spontaneous cure.' The rest became 'carriers.' The study indicated that treatment which requires considerable time may merely be carrying the children through the period during which they develop spontaneous cures, and that some children recover regardless of the type of treatment used." From this and other similar reports it is apparent that chemotherapy in its present development does little for the cure of gonococcal vulvovaginitis.

Meningitis

Until the advent of the sulfonamide drugs the treatment of meningitis, except in the epidemic cerebrospinal variety, was very unsatisfactory and usually futile, consisting essentially of the treatment of symptoms. With the coming of the sulfonamides the picture changed radically, although in tuberculous menin-

gitis, as in other forms of tuberculosis, the sulfonamides are without value. An example of the changed picture is seen in purulent meningitis, which formerly in nearly every case ended fatally. Now with sulfonamide therapy recoveries are commonplace. *Pneumococcus meningitis* generally responds favorably to the sulfonamides, particularly sulfapyridine and sulfathiazine, and *influenzal meningitis* to a less degree, but many observers feel that results are better in the latter type when sulfapyridine or sulfathiazole is given in combination with serum.

The wisest course in meningitis would seem to be the institution of chemotherapy with the sulfonamides in every case of meningitis, regardless of which type it may turn out to be, even though all cases will not respond to it.

Meningococcic Meningitis: *Harries*¹⁸ reports 500 cases treated by chemotherapy alone without intrathecal serum. Sulfapyridine was used in 431 cases and sulfathiazole in the remaining 29. Sulfathiazole appeared equally effective in bringing about recoveries and did not give rise to the toxic manifestations of sulfapyridine, nausea, and vomiting. The sulfonamide was administered by giving 2 Gm. by mouth, followed by 2 Gm. every four hours for four doses, and then 1 Gm. every four hours for 96 hours. After this 0.5 Gm. was given every six hours for another three days. Children under 12 years received half the adult dose and infants under 12 months one-quarter.

Lumbar punctures were made for the relief of headache. In all cases fluids were pushed in the form of five per cent glucose in saline solution. Acute septicemic cases were given desoxycorticosterone acetate intramuscularly. No case was considered out of danger until the spinal fluid sugar had returned to normal.

Campbell¹⁹ favors serum in combination with the sulfonamides. He reports 20 deaths in 40 patients treated with serum alone, and no deaths in ten patients treated with sulfanilamide and serum.

Antimeningococcus serum is recommended for intravenous use for patients who fail to improve sufficiently after 24 to 48 hours of adequate chemotherapy and earlier in selected cases

of severe or fulminating disease. The dose is empiric. About 50 to 100 cc. are given initially to an adult of average weight and subsequent doses depend upon the initial response. Intrathecal therapy may be given 24 hours after the intravenous injections have been started if the infection persists.

The Surgeon General of the United States Army in a circular letter²⁰ recommends the use of sulfadiazine. If this drug is not available, sulfanilamide is recommended.

Dingle and Finland,²¹ although favoring sulfapyridine at present, believe that sulfadiazine will be the drug of choice if experience with it proves its value, because it has the widest range of effectiveness, the lowest toxicity, and good penetration into the cerebrospinal fluid.

The plan of treatment they advocate follows: There should be immediate institution of chemotherapy after the presence of organisms, the preponderance of polymorphonuclear cells, or the occurrence of pus in the cerebrospinal fluid is recognized. Their preferred drug, as has been stated, is sulfapyridine. If given intravenously they use an initial "loading" dose of 0.1 Gm. per kg. of body weight of the sodium salt in distilled water, or in a concentration of two per cent or less in physiologic salt solution. A concentration of 0.5 per cent in saline solution is preferable, because it also serves to provide fluid to combat the dehydration.

If the parenteral route is used a similar total daily dose is given for the first two days. Drugs may be given parenterally for longer periods to patients with severe or fulminating disease, to those who are comatose, or to those who vomit excessively. The total daily dose may be given in three divided doses at eight-hour intervals.

After the first two days the drug was given by mouth. A similar dose is divided into four to six equal amounts and spaced evenly throughout the 24 hours.

Dehydration is checked by administering 3500 cc. of normal saline solution with or without five per cent dextrose solution.

Mutch²² reports on a new sulfonamide, sulfonamide ethyl-alpha-sulfonate, which he used successfully in the treatment of meningococcic meningitis. The drug is freely soluble in water and almost tasteless. Infants and patients in coma or those who are vomiting or have diarrhea can be treated easily by giving the drug by mouth, nasal tube, rectal tube, or intravenous drip. In the patients receiving the drug general malaise was slight and pallor, nausea, and vomiting never occurred. Cyanosis was common, but it never caused distress or required the discontinuance of therapy. Granulocytopenia or simple leukopenia was not encountered. Minor degrees of anemia were observed, but not with greater frequency or severity than is usual after a severe infectious illness. There were no serious complications.

The author treated 34 cases of acute epidemic cerebrospinal meningitis with the new drug. Three died, but there were no deaths among those seen in the first week of illness and who remained free from serious secondary infections of the viscera. The temperature of some patients was normal after 36 hours of treatment. Recovery was complete in as little as two and one-half weeks.

Influenzal Meningitis: The prevailing opinion is that both a sulfonamide (sulfapyridine or sulfathiazole) and serum should be used. The serum is given intravenously for all patients with type B infections. The initial dose of unconcentrated rabbit antiserum is 1.0 to 2.5 cc. per kg. of body weight, or the equivalent of 50 to 100 mg. of antibody nitrogen, depending upon the severity of the infection. Intrathecal injections of antiserum with complement only are used for patients who fail to respond within 48 hours after intravenous serotherapy is begun.

Pneumococcal Meningitis: Sulfapyridine and sulfadiazine are considered the most effective sulfonamides for pneumococcal meningitis. Hollander²³ made an extensive review of 260 reported cases of pneumococcal meningitis in which sulfonamide therapy, with or without serum, was employed in an attempt to evaluate the effectiveness of each therapeutic agent alone and combined. Sulfapyridine proved the most effective drug in 160

cases in which chemotherapy was used alone. The percentages of recovery with sulfapyridine-serum therapy and with sulfapyridine alone are the same, 58 per cent. Meningitis caused by types III and V seemed to require the combined therapy. Also, the combined therapy gives the best prognosis in the age period between 10 and 20 years.

The serum is begun for all patients as soon as the type of the causative pneumococcus has been determined, but particularly for those who do not respond favorably to sulfonamide therapy alone after 24 to 48 hours. The initial dose is usually 200,000 units and the mode of administration is by vein.

Hodes, Smith, and Ickes²⁴ report on 60 cases of pneumococcal meningitis treated with sulfonamides. As soon as the diagnosis of meningitis is established by the presence of cloudy spinal fluid a blood culture and nasopharyngeal cultures are obtained and the patient is then given the sodium salt of one of the sulfonamides intravenously. Children are given 0.025 to 0.050 Gm. per kg. of body weight of the sulfonamide by mouth or, if unconscious, by stomach tube. From then on approximately 0.2 Gm. per kg. of body weight is given every 24 hours, divided into six or eight doses. Adults usually receive 3 Gm. intravenously and 2 to 4 Gm. by mouth as an initial dose, and 1.5 Gm. every four hours thereafter. During the early period of treatment the blood level of the sulfonamide is determined daily. The authors believe that levels of 8 to 12 mg. per cent work as well as higher levels, and rarely give the drug intravenously after the first dose. The sulfonamide is usually continued for two weeks after the temperature has dropped to normal. It is not withdrawn unless the spinal fluid is sterile and has a normal sugar content and the patient appears well. Some of the patients showed definite clinical improvement within 24 hours of admission, but others who eventually recovered remained ill for as long as ten days.

Eleven of the 60 patients showed some toxic effects from the sulfonamides. Six of these developed gross or microscopic hematuria. When this occurred early in the course of the disease the

patient's fluid intake was increased and the hematuria cleared. When blood appeared in the urine at a time when the patient was clinically well drug therapy was discontinued. Two of the patients developed "drug fever," one a drug rash, and two showed leukopenia. All of the latter manifestations of sensitivity to the drug occurred during convalescence and not one was fatal.

An interesting angle to this report was the high mortality in children under two years of age compared with children over two years of age, only 22 per cent of the children in the first group recovering in contrast with 64 per cent of the older group.

Streptococcic Meningitis: Rantz²⁵ reports four cures of streptococcus meningitis with sulfapyridine and feels that this drug is effective in nonhemolytic or viridans streptococcic meningitis. *Intravenous therapy with antistreptococcus or scarlet fever convalescent serum may be tried for patients who still have infected cerebrospinal fluid after 48 hours or more of adequate chemotherapy.* However, the value of these sera is questionable.

Riley and Waugh²⁶ favor the use of sulfadiazine in streptococcic meningitis and state: "The effectiveness of sulfadiazine as a therapeutic agent, coupled with its low toxicity, makes this the drug of choice in the treatment of streptococcic meningitis."

Torula Meningitis: All treatment for torula meningitis heretofore has been ineffective, but a recent report by Marshall and Teed²⁷ tells of the recovery of a case of this disease treated with sulfadiazine. *It is possible, therefore, that the mycoses may be amenable to sulfonamide therapy.*

Osteomyelitis

The therapy of acute osteomyelitis has resolved itself into the following measures: Rest, blood transfusions, fluids, sulfonamides, serotherapy bacteriophage, antitoxins, immunotransfusions, and local treatment. Long and Bliss²⁸ state: "We have yet to see a patient suffering from the acute form of this disease whose infection was not cured when adequate therapy with sulfanilamide was instituted."

The effectiveness of the sulfonamides is high when the infection is caused by the streptococcus, gonococcus, or meningococcus. Their value in other types of osteomyelitis has yet to be proved, but one should institute sulfonamide therapy in every case, at least until the type of organism has been demonstrated to be one not likely to be affected by these drugs. Certainly, in infants, there is at least an even chance that the offending organism is the streptococcus, and infants tolerate the sulfonamides very well.

Schmidt^{28a} reports four cases which illustrate sulfonamide therapy for osteomyelitis in children:

CASE 1: R. Z., an 11-year-old boy, was admitted to the Milwaukee Children's Hospital on December 4, 1911. The mother stated that the child had struck his left leg against a cement block five days before. The pain increased daily. On admission he was complaining bitterly of pain in the left knee. Past history is of no significance.

Examination: On admission, the patient appeared acutely ill and presented a typical picture of an acute pyogenic infection. His lips were parched, and the skin was dry. He was rational. He cried continuously, fearing that someone would touch his leg. The lower one-half of the femur, including the knee, was swollen. There was no fluctuation. Tenderness was exquisite on both the medial and lateral aspect of the lower end of the femur. The knee could be moved through an arc of 30 degrees with but slight discomfort. The rectal temperature was 103.8° F., pulse rate 112, and respiratory rate 28. The leukocyte count was 20,800, the erythrocyte count 5,200,000, and the hemoglobin 11.5 mg. The urine was negative.

A roentgenogram of the femur was essentially negative. Blood culture taken on December 5 revealed a hemolytic *Staphylococcus aureus*.

Diagnosis: Acute osteomyelitis of the left femur.

Treatment: Sulfadiazine was started immediately on the basis of 1 grain per pound of body weight per day. This was increased to 1¼ grains on the third day and was decreased to ½ grain on

the ninth day. After the patient's temperature had been normal for 12 days and the sulfadiazine discontinued, it was interesting to note that the following day the temperature started rising, and the third day it was 101.5° F. He was again given sulfadiazine at the rate of 1 grain per pound of body weight per day for one week, after which the amount was reduced to ½ grain. On January 16, which was one month after the fever originally subsided, the sulfadiazine was again discontinued, only to be followed with a rising temperature and pain in the affected thigh. It was then decided that we would continue with the sulfadiazine and maintain a blood level from 3 to 7 mg. per 100 cc. for a period of at least two months. The sulfadiazine was finally discontinued four months after admission to the hospital.

Two hundred fifty cc. of citrated blood were given daily the first four days in the hospital, and in addition the patient received 250 cc. of five per cent dextrose intravenously on the second and third day. He probably had a reaction to the transfusion on the third day. His temperature rose to 106° F. Hot fomentations were applied to the leg during the acute stage. On admission, Russell's traction was applied to the leg.

A roentgenogram on December 13, 1941, showed an osteomyelitis of the left femur. He was discharged from the hospital on April 20, 1942.

Summary of Case: This is a typical case of an acute hematogenous osteomyelitis that was treated with sulfadiazine plus other supportive measures. There were two flare-ups following the discontinuation of sulfadiazine at too early a date. Clinically he has completely recovered.

CASE 2: D. P., a 10-year-old girl, was admitted to Milwaukee Children's Hospital on January 7, 1942. This patient had had an earache about two weeks prior to admission. On January 5, she developed a backache, which was followed with a chill. Past history is of no significance.

Examination: Examination revealed a well-developed girl complaining bitterly of pain in the back. Examination was most difficult because of the marked muscle spasm of the extensor

muscles of the hip and the posterior muscles of the back and neck. The picture was that of an acute meningeal irritation. There was no swelling over the spine, but tenderness was rather generalized over the lumbar region. The abdominal reflexes were present. The reflexes in the upper extremities were somewhat hyperactive, but the knee jerks and Achilles' reflexes were definitely hyperactive. The plantar reflexes were negative. There was no ankle clonus. A few drops of pus were aspirated from the most tender area on January 8. The culture revealed hemolytic *Streptococcus aureus*. A cisternal puncture on January 8 revealed 233 cells and a trace of globulin. The rectal temperature on admission was 101.6° F., pulse 126, respiration 26. The leukocyte count was 15,000, and the hemoglobin was 10.5 mg. A roentgenogram of the spine was negative.

Diagnosis: Osteomyelitis of the spine.

Treatment: On January 8, the patient received sulfadiazine on the basis of 1 grain per pound of body weight per day. On the evening of the third day in the hospital she passed gross blood in the urine, which subsided immediately when the dose was reduced one-half. A superficial abscess over the third lumbar vertebra was incised on the tenth day and continued to drain for three and one-half months. One month after admission, the dosage of sulfadiazine was again reduced in an attempt to maintain a blood level of 3 to 7 mg. for an additional three months. On the third day in the hospital she received a transfusion of 200 cc. and on the fourth day 500 cc. of citrated blood. A roentgenogram on January 21 revealed an osteomyelitis of the spinous process of the third lumbar vertebra. She was discharged from the hospital on January 24.

Summary of Case: This patient developed a hematuria probably due to the large doses of sulfadiazine. The hematuria cleared up immediately when the dose was cut in half. The abscess was incised immediately after the acute stage and drained for three and one-half months. Clinically, this patient has made a complete recovery.

CASE 3: C. B., a 4-year-old girl, was admitted to St. Luke's Hospital on January 21, 1942. According to the father, the patient had struck her leg on a door four days prior to admission. Two days later she complained of pain in the left ankle. Past history is inconsequential.

Examination: This child had the typical appearance of a person with an acute pyogenic infection. The lower one-third of the left leg was swollen. The ankle was slightly enlarged, but it could be moved slowly without much discomfort. There was local heat and tenderness about the lower end of the tibia. The rectal temperature on admission was 102.6° F., pulse rate 128, respiration 30. Blood culture taken on January 22 revealed hemolytic *Staphylococcus aureus*.

A roentgenogram on admission was negative.

Diagnosis: Acute osteomyelitis of the left tibia. A roentgenogram on February 2 revealed an osteomyelitis of the left tibia.

Treatment: Even though the patient received sulfadiazine on the basis of 1 grain per pound of body weight per day beginning January 22, the blood level on January 23 and 24 was only 3.5 and 5.3 mg., respectively, per 100 cc. On January 26, it was 10 mg. On the fourth day she began to show some improvement. During hospitalization the sulfadiazine dosage remained the same, but the following two months an attempt was made to keep the blood level between 3 and 7 mg. per 100 cc. A superficial abscess just below the knee was drained on January 31. It was completely healed one month later at the time the cast was removed. She was discharged from the hospital on February 7.

Summary of Case: This case was unusual in that even though large doses of sulfadiazine were given, the blood level did not rise above 5.3 mg. per 100 cc. until the third day. The abscess was incised when the temperature was practically normal, and it was completely healed in less than four weeks. Clinically, she has made a complete recovery.

CASE 4: R. E., a boy aged two years and four months, was admitted to Milwaukee Children's Hospital on April 24, 1942. According to the mother, the child had had impetigo for several months. He had complained of pain in the left leg for one week. Past history was of no significance.

Examination: This patient did not appear acutely ill. The lower one-half of the left thigh presented some swelling. It was difficult to localize the tenderness. The rectal temperature on admission was 103° F., pulse 135, respiration 25. Blood culture on two occasions was negative. Throat culture revealed hemolytic streptococcus. The leukocyte count was 21,300, the erythrocyte count 4,450,000, and the hemoglobin was 10.5 mg. A roentgenogram of the femur was negative.

Diagnosis: Acute osteomyelitis of left femur.

Treatment: Sulfadiazine on the basis of 1 grain per pound of body weight was given immediately on admission. The dosage was reduced by one-half after 14 days of hospitalization. Because of a rising temperature, five days later a full dosage was again given for an additional ten days. Following this, the patient received one-half the full dose for a period of two months. A transfusion of 200 cc. of citrated blood was given on May 16 and again on May 19. Russell's traction was applied on admission to the hospital. A roentgenogram on May 2 revealed an osteomyelitis of the left femur. He was discharged on July 28.

Summary of Case: In spite of large doses of sulfadiazine, the temperature remained elevated for two weeks. After subsiding for just two days, it again rose for a period of ten days. Clinically, the patient has made a complete recovery.

Otitis Media and Mastoiditis

Otitis Media: Sulfonamide therapy has its greatest effectiveness in the acute infections and particularly before suppuration has started. Sulfanilamide has had the most use of the various sulfonamides, and a sharp reduction in the incidence of mastoiditis requiring operation following its administration has been reported by Bowers²⁹ and by Horan and French.³⁰ However,

otitis of pneumococcal or staphylococcal origin had better be treated by sulfapyridine or sulfathiazole. Sulfadiazine can be used in all cases and may be preferable because of the rapidity of reaching a blood concentration and because of its low toxicity.

DeSanctis and Larkin³¹ reported on 1992 cases of otitis media and mastoiditis over an 11-year period, many of the cases since 1937 being treated with sulfonamides. Their summary and conclusions follow: (1) Over an 11-year period 1992 children with otitis media and mastoiditis were admitted to the babies' wards of the New York Postgraduate Hospital; (2) the 932 cases in the last six years, 1936 to 1941, were studied in great detail as to age, sex, and seasonal variations, the symptoms and physical signs of otitis media and mastoiditis, and the relative frequency of each; (3) a year-by-year breakdown of symptoms, physical signs, and laboratory data reveals that there has been no decrease in the severity of otitis media and mastoiditis in the last few years; (4) there has been a decrease in the reliance of irrigations of the ear and myringotomy in the treatment of otitis media; (5) a comparison of the group of patients treated with sulfonamides against the group treated without sulfonamides from 1937 to 1941 shows an incidence of mastoiditis of nine per cent in the former and 30 per cent in the later; (6) sulfathiazole is the drug of choice. One grain per pound a day is the recommended dosage.



(DeSanctis, A. G., and Larkin, V. de P.: *J. A. M. A.*)

Chart 1—Age incidence in a series of 932 cases of otitis media and mastoiditis (1936-1941).

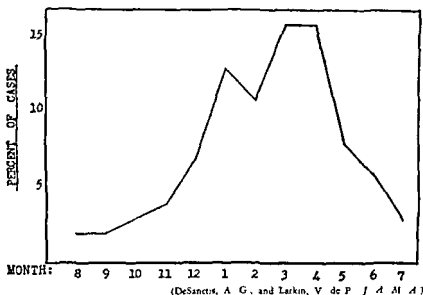


Chart 2—Monthly variation in incidence in a series of 932 cases of otitis media and mastoiditis (1936-1941).

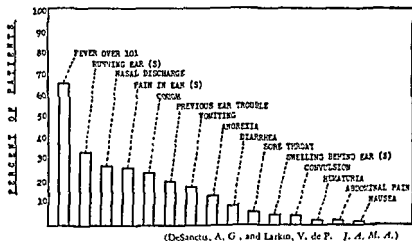


Chart 3—Symptoms of otitis media and mastoiditis.

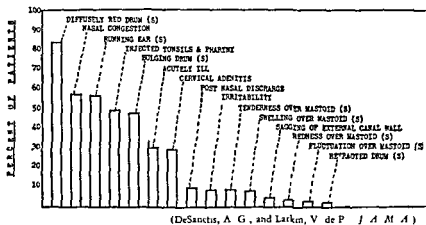


Chart 4—Physical signs of otitis media and mastoiditis.

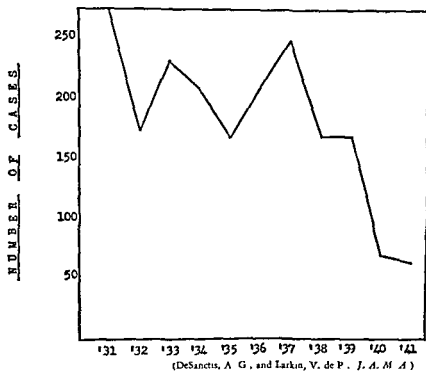


Chart 5—Incidence of otitis media and mastoiditis (1931-1941).

In the discussion of this paper, Larkin stated that he felt it had been proven conclusively "that the one responsible agent which has produced these remarkable changes in the incidence of mastoiditis is chemotherapy."

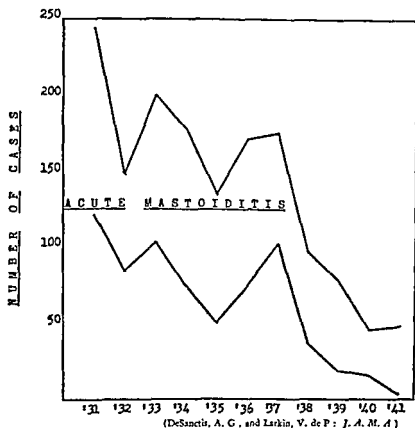


Chart 6—Comparison of incidence of acute purulent otitis media and of acute mastoiditis (1931-1941)

Forty patients with otitis media received chemotherapy and 20 were treated without drugs in a report by Curtin.³² This report shows a ten per cent statistical advantage in favor of chemotherapy. Also, it is shown that chemotherapy can shorten the course of the disease and prevent many complications. For streptococcic infections a large initial dose of 1.6 to 2 Gm. (25

to 30 grains) of sulfanilamide should be given every four hours for three or four days. If the temperature drops and the discharge diminishes, the daily dose can be reduced to 2.6 to 3.2 Gm. (40 to 48 grains) for a few days and then to 1.3 Gm. (20 grains) a day for a few days. Chemotherapy should be continued for six or seven days after the symptoms subside to avoid a recurrence.

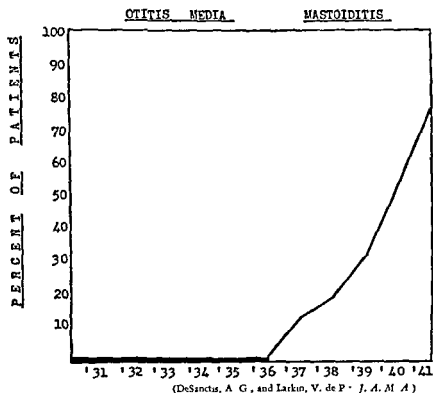


Chart 7—Treatment of otitis media and mastoiditis with the sulfonamides.

For pneumococcic infections, smaller doses of sulfathiazole are given. Actually ill children receive 0.13 Gm. (2 grains) per pound, followed by a maintenance dose of 0.065 Gm. (1 grain) per pound. If the desired results are not obtained, the level of the drug in the blood should be checked, since it does not become optimal with this dose in some patients. A valuable addition to chemotherapy sometimes is antibacterial serum.

Mastoiditis: If sulfonamide therapy is started before bone destruction occurs, there is a diminution in the duration of the discharge and a reduction in the frequency of mastoid operations. Bowers²⁹ places this reduction at 50 per cent if therapy is adequate. He advises against chemotherapy after uncomplicated mastoidectomy, but states that complicated mastoidectomy requires intensive chemotherapy.

Maybaum *et al.*^{33, 34} believe that sulfonamide should be used cautiously if at all in acute otitis media, because it may obscure the clinical picture of the ensuing mastoiditis and give rise to a latent course of the disease with the possibility of dangerous complications. Their only use for the drug in otitis media is in such complications as meningitis, sinus thrombosis, and brain abscess. On the other hand, Hampsey³⁵ feels that in spite of its masking effect it should be used, because it tends to localize the infection and prevents systemic invasion by the infecting organisms. Recent work indicates that sulfadiazine, sulfapyridine, and sulfathiazole are as effective as sulfanilamide in these infections, various writers having a preference for one or another of the sulfonamides.

Sulfadiazine was the sulfonamide of choice of Tucker and Flake³⁶ in the management of a controlled series of mastoidectomy wounds. In 16 group A patients the wound of a complete simple mastoidectomy was closed without drainage with sulfadiazine poured in, that of 15 group B patients was sutured without drainage, but the patients received sulfadiazine orally, and that of 15 group C patients was only drained. The hospitalization period for group A and B patients averaged around ten days. The wounds healed primarily and the tympanic membrane *was healed and dry at this time. The wound of only one group B patient broke down. The group C patients had the usual prolonged convalescence, and their average hospital stay was 21 days, as compared to 10 and 9 days, respectively, for groups A and B patients.*

Peritonitis

Primary peritonitis caused by the pneumococcus or the hemolytic streptococcus is not uncommon in infancy and has always had a very high mortality rate. Sulfonamide therapy is indicated in all of these cases, but there are differences of opinion as to the technic of treatment.

Alford³⁷ favors early surgical drainage, followed immediately by chemotherapy and specific antiserum in suitable cases. Denzer,³⁸ on the other hand, believes that surgery is contraindicated once the diagnosis is made and states: "Results of treatment with sulfanilamide without operation were far better than when operation was performed and sulfanilamide was given subsequently."

Drugs of the sulfonamide group other than sulfanilamide have not had wide usage in this condition, but it would seem that sulfadiazine would be effective since it is useful against both the pneumococcus and the hemolytic streptococcus.

For the peritonitis complicating appendicitis, see the section on *Appendicitis*, page 97.

Pneumonia

As in pneumonia in adults, sulfonamide therapy has had a marked effect on the treatment of pneumonia in children. The mortality from pneumococcus pneumonia in children over two years of age has always been low, but sulfapyridine and sulfathiazole have caused a sharp drop in the already low figure. Furthermore, as stated by Silverthorne, Brown, and Auger,³⁹ chemotherapy has shortened the course of pneumococcus pneumonia in this age group.

The mortality from pneumococcus pneumonia in children under two years of age has been about four times that in the older group. Here sulfapyridine or sulfathiazole are even more urgently needed, for it is difficult to do sputum typing, the finding of several types of pneumococcus is common, and the administration of serum intravenously is far from easy.

In pneumonia complicating measles and whooping cough, Thompson and Greenfield⁴⁰ report a marked reduction in its

incidence when sulfonamides are given in prophylaxis. Peters⁴¹ also reports a reduction in mortality of 80 per cent with sulfapyridine, as compared with the experience of previous years in the bronchopneumonia complicating whooping cough. Sulfathiazole gave excellent results in the bronchopneumonia of whooping cough in a series of 71 children reported by Frank, Patton, and Hamilton.⁴² The drug was given until average blood levels of 2 to 3 mg. per cent were reached. Four per cent of this group died and, of these, two were infants less than one year of age. In a previous study, hyperimmune serum had been used in the treatment of 30 patients with a mortality rate of 20 per cent. In another group of 16 patients treated with sulfapyridine the mortality rate had been 25 per cent.

TABLE 4—DOSAGE OF SULFAPYRIDINE FOR INFANTS AND CHILDREN WITH PNEUMOCOCCAL PNEUMONIA
Used in 1938 and 1939 by Barnett, Hartmann, Perley, and Ruhoff
(*J. A. M. A.* 112:518, 1939)

Age	Dose	Interval
1 to 3 months	0.15 Gm.	Every 4 hours
6 months to 1 year	0.3 Gm.	Every 4 hours
2 years	0.3 Gm.	Every 3 hours
5 years	0.6 Gm.	Every 4 hours
12 years	0.9 Gm.	Every 4 hours

(*Physicians' Bulletin* Eli Lilly and Co.)

Rheumatic Fever

Prophylaxis: There is no known method of active immunization against rheumatic fever comparable to smallpox vaccination, nor is there any test of susceptibility like the Schick test in diphtheria. However, Coburn and Moore⁴³ and Thomas and France⁴⁴ have published their experience with sulfanilamide as a prophylactic measure against rheumatic fever.

Coburn and Moore found that if they gave the drug from November to June to rheumatic children they would be protected against recurrences of the disease.

Thomas and France administered 1 to 1.3 Gm. (15 to 20 grains) daily of sulfanilamide to 30 rheumatic children over 14 years of age during the late fall, the winter, and the spring. Drug levels ranged from 1.0 to 5.5 mg. per 100 cc. of blood and toxic reactions were mild and infrequent. None of this group developed any hemolytic streptococcic infections nor a severe recurrence of the rheumatic fever. In a control group of 30 patients, who did not receive sulfanilamide, there developed one severe hemolytic streptococcic infection, five major rheumatic attacks, and three acute illnesses possibly of a rheumatic nature.

Treatment: Sulfonamide drugs are contraindicated during the acute phases of rheumatic fever since they commonly induce significant toxic reactions. Swift, Moen, and Hirst⁴⁵ and Massell and Jones⁴⁶ have published papers showing that not only are the incidence of toxic reactions from sulfanilamide high and the benefits negligible, but that frequently the drug makes the patient worse.

Pyuria

Robbin,⁴⁷ in a report of the treatment of 200 cases of pyuria in infants and children, states: "The advent of the sulfone compounds has revolutionized the treatment of acute pyuria and has greatly helped in the treatment of chronic pyuria. Sulfanilamide was at first solely used. The dangers and contraindications to its use are well known. Suffice it to say that by its use in many cases of pyuria, even when the disease was discovered late, the urine was cleared and the clinical symptoms abated within 24 hours. In very severe infections similar results were obtained in from four to seven days. Always, it may be stated, the abatement of the symptoms was dramatic. In the several instances in which the *streptococcus fecalis* was cultured, the pyuria did not respond to sulfanilamide, but was cleared by the use of mandelic acid. In all instances in which sulfanilamide was given, the dose was one grain per each pound of weight. One-quarter of the total was given as an initial dose, the rest was divided so as to be given in equal amounts at four-hour intervals during both day and

night. Originally, daily blood counts and differential stains were made of the white cells of the peripheral circulation, but at present only occasional counts, as the clinical condition indicates, are made. During the past year, sulfadiazine (2-sulfanilamidopyrimidine) has replaced sulfanilamide as the drug of choice in pyuria. The dosage and manner of administration remain the same.

Scarlet Fever

Gordon, Solomon, and Pearlman⁴⁸ made a comparison of the relative effectiveness of sulfanilamide and antitoxin in the treatment of scarlet fever on 680 patients. The patients were divided into mild and moderately ill groups, and each of these groups was subdivided into four parts, so that one series received no specific treatment, the second series received sulfanilamide, the third was given scarlet fever antitoxin, and the fourth had a combination of sulfanilamide and scarlet fever antitoxin. The sulfanilamide was administered in daily doses of one grain per pound of body weight until the temperature dropped to less than 37.8° C. (100° F.), and then the dosage was cut in half until the patient had been treated for two weeks in all.

The scarlet fever antitoxin was given intramuscularly in doses of 9000 units and a small amount of adrenalin was injected at the same time.

Sulfanilamide was more effective than the antitoxin in reducing the incidence of complications, but the combination of sulfanilamide and antitoxin gave better results than either did alone. About 20 per cent of the patients receiving sulfanilamide developed reactions, which consisted chiefly of rashes developing between the ninth and eleventh day after the treatment had been started. Only 3.6 per cent of the patients who received scarlet fever antitoxin alone developed serum sickness and this was mild in almost every instance.

Top and Young⁴⁹ compared sulfanilamide, convalescent serum, and scarlet fever antitoxin in a series of 390 patients with scarlet fever. These were divided into three groups, comparable

in respect to age, the season of the year in which they became ill, the stage of the disease, and the severity of the infection. Each group received one of the therapeutic agents being tested, the convalescent serum in one dose of 30 cc. intramuscularly, the antitoxin in one dose of 6000 units, and the sulfanilamide in doses varying with the weight of the patient. The effectiveness of the treatment was judged on the basis of the need for other medication, the number and severity of complications, and the duration of the hospital stay. The patients receiving human convalescent serum seemed to make the best progress, but an analysis of the figures did not indicate significant differences which might not have arisen from chance alone.

Tonsillitis

Hopkins⁵⁰ gave sulfanilamide or sulfapyridine to 49 patients with tonsillitis due to the hemolytic streptococcus without favorable results. In fact, complications were more frequent in the treated group than in those who did not receive the sulfonamides. Two patients undergoing treatment with sulfapyridine acquired streptococcic tonsillitis. Neither was the carrier state influenced by the drugs. Theoretically the sulfonamides should be effective in streptococcic tonsillitis, but apparently there are certain factors entering into the problem which prevent favorable action.

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CHOLERA

Chopra *et al.*¹ report a marked decrease of mortality (6.38 per cent to 3.21 per cent) in cholera from the use of sulfaguanidine. In addition to this favorable result, they state that the patients receiving sulfaguanidine passed fewer stools per day and required less intravenous saline.

TABLE 1—THE COMPARATIVE VALUE OF DIFFERENT DOSES OF SULFAGUANIDINE COMBINED WITH HYPERTONIC SALINE ON THE ONE HAND AND SALINE THERAPY ON THE OTHER HAND

	Initial Dose 0.5 Gm Maintenance Dose 0.25 Gm Every 6 Hours for 72 Hours				Initial Dose 1 Gm Maintenance Dose 0.5 Gm Every 6 Hours for 72 Hours				Control Cases with 1. V Saline Perfusion Only			
	Number Treated	Number Cured	Number Dead	Mortality Percentage	Number Treated	Number Cured	Number Dead	Mortality Percentage	Number Treated	Number Cured	Number Dead	Mortality Percentage
Culturally positive . . .	26	25	1	3.84	54	52	2	3.70	67	61	6	8.97
Culturally negative ..	9	9	0	0.00	42	42	0	0.00	7	7	0	0.00
Clinically positive	266	248	18	6.76	122	117	5	4.09	20	20	0	0.00
Totals	301	282	19	6.31	218	211	7	3.21	94	88	6	6.38

On the other hand, Carruthers² states: "It may be concluded that sulfaguanidine has no demonstrated value in the treatment of cholera."

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COLONIC SURGERY

Poth¹ reports on the use of succinylsulfathiazole preoperatively and postoperatively in surgery of the large bowel in 250 patients. The coliform bacterial population of feces, he says, normally varies between 1,000,000 and 100,000,000 per Gram of wet stools. The number of gram-negative and gram-positive flora is roughly equal and usually varies from 100,000,000 to 10,000,000,000 organisms per gram of wet feces. When succinylsulfathiazole is administered in effective therapeutic doses, the gram-positive and gram-negative organisms decrease in number at approximately the same logarithmic rate for a few days until the gram-positive population becomes constant. The number of gram-positive bacteria continues to fall. The latter decrease is not due solely to the change in the number of coliform organisms (Chart 1). The bacteriologic identification of the different organisms making up these groups has not been practical because of the many different varieties of bacteria involved.

Proof is cited that succinylsulfathiazole has bactericidal as well as bacteriostatic action against *Escherichia coli* (Chart 2).

The author gives the following preoperative preparation to all patients whose intestine is not completely obstructed and who require operations on the large bowel: The patient is put on a low residue diet and receives succinylsulfathiazole in a dosage of 0.5 Gm. per kg. of body weight during the first day and 0.25 Gm. per kg. thereafter, divided into six equal doses and administered at four-hour intervals. No enemas or purga-

tives are given. Usually in the course of three to seven days the stools will become small in bulk, semifluid, and relatively odorless. A bacteriologic examination of the feces will show the bacterial flora to be significantly altered. By now the patient's abdomen is flat and the bowel is free from gross fecal material or gas.

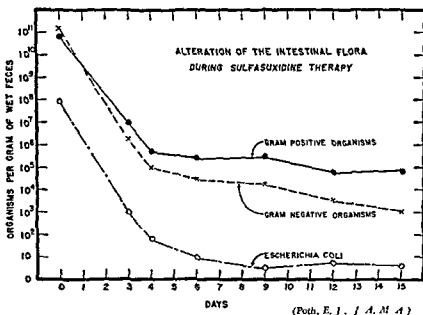


Chart 1—Alteration of the bacterial flora in the bowel following the administration of succinylsulfathiazole. Before therapy is begun in this instance the total gram-positive and gram-negative organisms each number approximately 10^{11} and the *Escherichia coli* number about 10^8 . Thus the total gram-negative organisms initially exceed the number of *Escherichia coli* by practically 10^{11} , while after 15 days of treatment the difference is roughly a thousand. Also the total gram-positive organisms surviving after therapy are only one-millionth of their original number.

Experience has demonstrated that when the *Escherichia coli* count has dropped to 1000 and the other significant alterations in the feces have taken place, the bowel is properly prepared for operation. If, however, distention continues, the feces do not change their physical characteristics and the bacterial flora is not altered, the bowel is not properly prepared for operation. The usual causes for failure are intractable diarrhea and the

administration of liquid petrolatum. The diarrhea can usually be controlled with opiates and liquid petrolatum should be withheld. Attention is directed to the fact that opiates given to control a severe diarrhea will not cause an accumulation of fecal material while the patient is on a low residue diet and is receiving therapeutic doses of succinylsulfathiazole. This regimen of preoperative treatment has always resulted in a clean bowel,

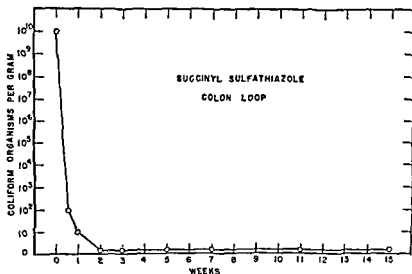


Chart 2—Action of succinylsulfathiazole in an isolated loop of the descending colon of the dog. Five Gm. of succinylsulfathiazole introduced into the segment of bowel at the time of operation reduced the number of coliform organisms to zero in two weeks and could not be recovered again during the course of the experiment. Solid drug was always present in the loop to indicate that the drug is slowly absorbed from the colon. (Puth, E J J A M A)

and it has not been necessary to abandon a planned operative procedure because of an unsatisfactorily prepared colon. This regimen has the advantage of causing no dehydration of the patient just prior to operation as well as removing the bulk of pathogenic bacteria.

The 50 patients in Table I received succinylsulfathiazole preoperatively until the stools were semifluid, small in bulk, and relatively odorless, and the coliform bacteria were reduced to

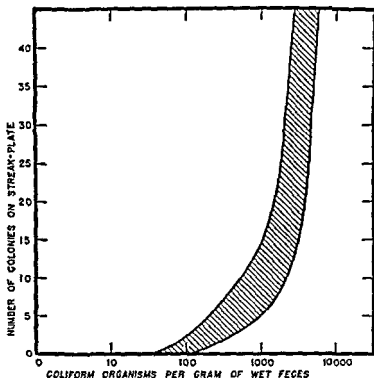


Chart 3—The use of a platinum loop which will transfer approximately 0.01 Gm of fecal matter to streak a desoxycholate agar plate is sufficiently accurate to indicate when the bacterial flora have been significantly altered. Example: When the coliform count has been reduced to 1000, the colony count on the streaked plate will vary from 5 to 15. (Poth, E. J.: *J. A. M. A.*)

TABLE 1—PATIENTS GROUPED ACCORDING TO CONDITION

Condition	Patients
Carcinoma of right colon.	7
Carcinoma of transverse colon.	3
Carcinoma of left colon	26
Fecal fistulas involving colon.	6
Chronic volvulus sigmoid.	1
Diverticulitis of colon.	2
Lesions of urinary bladder (transplantation of ureters into bowel)	3
Rectovesical fistula.	2
Total.	50

(Poth, E. J.: *J. A. M. A.*)

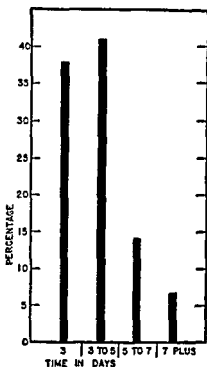


Chart 4—Length of succinylsulfathiazole therapy required to effect a significant alteration of the bacterial flora in the bowel. The seven per cent of cases requiring more than seven days include those cases which present special circumstances unfavorable to the action of the drug as well as those instances which fail to give a satisfactory response. (Poth, E. J.: *J. A. M. A.*)

TABLE 2—OPERATIVE PROCEDURES INVOLVING THE LARGE BOWEL AND PERFORMED ON PATIENTS RECEIVING PREOPERATIVE AND POSTOPERATIVE TREATMENT WITH SUCCINYL-SULFATHIAZOLE

Operation	Number of Cases
Abdominal-perineal resection (Miles).	16
Resection of sigmoid, primary anastomosis	14
Resection carcinoma of transverse colon, primary anastomosis	3
Resection of cecum, ascending colon, ileocolostomy	7
Resection of fecal fistula	6
Ureterosigmoidostomy	3
Repair of rectovaginal fistula	1

(Poth, E. J.: *J. A. M. A.*)

1000 or less per gram of wet feces. The drug was administered postoperatively as soon as the patient tolerated 30 cc. of warm water by mouth and was continued as long as 12 days in those instances in which primary suture of the bowel had been done.

The postoperative course of these patients as a group was unusually smooth. Some of the patients had moderate gaseous distention, but troublesome, extensive abdominal distention did not occur and gas pains were ordinarily mild and of short duration. Although many of the intestinal anastomoses were performed by the open technic, postoperative peritonitis and deep abscess formation did not occur with one possible exception when, following the second stage of a difficult ureterosigmoidostomy, extravasated material gave the alpha *Streptococcus fecalis*. *Escherichia coli* was absent.

Toxic reactions coincident with the administration of succinylsulfathiazole are infrequent and mild. An occasional individual may complain of dizziness, headache, or loss of appetite. Hematuria, hemocytologic changes, and crystals of the drug in the urine have not been observed. With a single exception hyperpyrexia, vomiting, and erythema have not occurred.

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COMMON COLD

Internal medication with the sulfonamides is without value in the common cold, although there have been reports on the favorable influence of the sulfonamides on the nasal mucosa when applied locally. (See *Nasal Therapy*, page 253.) A recent tendency has been to give a sulfonamide in the common cold as a prophylaxis against pneumonia. Since the incidence of pneumonia arising from a common cold is only about 1 in 1000, it is scarcely good medical practice to subject so many persons to the dangers of drug sensitivity and toxicity for the rather rarely developing pneumonia. Furthermore, in the 0.1 per cent of

patients with colds who develop pneumonia many of them may have a virus pneumonia, against which the sulfonamides are useless, or a staphylococcic or hemolytic streptococcic pneumonia, against which the value of the sulfonamides is not fully proved. (See *Respiratory Tract Infections*, page 261.)



CONJUNCTIVITIS

See page 265



DACRYOCYSTITIS

See page 261



DERMATITIS HERPETIFORMIS

See page 171



DERMATOLOGY

Topical Sulfonamide Therapy

"Although the topical application of the sulfonamides proved to be definitely superior in the treatment of pyogenic skin conditions as compared with the older methods," says Strakosch and Clark,¹ "it nevertheless often falls short of our expectations and sometimes fails completely." Best results were obtained by these authors in very superficial pyogenic infections, such as impetigo contagiosa. Sometimes the topical application of sulfonamides aggravates the skin condition, some of these aggravations being due to the use of the sodium salts of sulfathiazole and sulfadiazine, which can cause chemical burns due to their strong alkalinity (pH 9 to 10 concentrations of one to ten per cent).

Failures from topical sulfonamide therapy also occurred even when the proper sulfonamide in its proper form was used. In

TABLE 1—COMPARISON OF THE EFFECT OF TOPICALLY APPLIED SULFATHIAZOLE, ALONE AND IN COMBINATION WITH UREA ON INFECTED DERMATOSES

KEY:
 L—Left
 R—Right
 SAT—sulfathiazole (Lederle)
 NaSAT—sodium sulfathiazole (*ibid*) CP—coagulase positive
 U—urea (Du Pont crystals)
 L—lactose (USP powder)
 H—Hydrosorb ointment-base (Abbott)
 Hem—hemolytic
 Strep—Streptococci
 Staph—Staphylococci

Case No	Sex	Age	Area Involved	Diagnosis	Treatment	Healing Time Comments
1	F	23	Both hands	Eczematoid dermatitis Hem. Strep	L hand 5% SAT, 30% U in H R hand 5% SAT in H	5 days 8 days
2	F	29	Both hands	Eczematoid dermatitis Staph. CP Hem. Strep	R hand 5% SAT, 30% U in H L hand 5% SAT in H	4 days 7 days
3	M	25	Both legs	Pyoderma Staph. CP.	L leg 5% SAT, 30% U in H R leg 5% SAT, in H	5 5 days 8 days
4	M	53	Face and neck	Eczematoid dermatitis Hem. Strep	R half 5% SAT, 30% U in H L half 5% SAT in H	5 days 9 days
5	M	51	Face and neck	Eczematoid dermatitis Hem. Strep	R half 5% SAT, 30% U in H L half 5% SAT in H	6 days 8 days
6	M	19	Both hands	Eczematoid dermatitis Hem. Strep Staph. CP	L hand 10% SAT, 20% L, 70% U, 1 part in 2 parts H ₂ O Wet packs R hand SAT sat'd in saline as wet packs	3 days Not much improvement after 5 days
7	M	29	Both hands	Pyoderma Hem. Strep Staph. CP	L hand 10% SAT, 20% L, 70% U, 1 part in 2 parts H ₂ O Wet packs R hand SAT sat'd in saline as wet packs	3 5 days 8 days
8	F	45	Both legs	Ecthyma Staph. aureus CP.	R leg 5% SAT, 30% U in H L leg 5% SAT in H	6 days 9 days
9	F	35	Both hands and forearms	Eczematoid dermatitis Staph. aureus CP	R arm 5% SAT, 30% U in H L arm 5% SAT in H	Improved after 3 days Rx discontinued No result after 5 days
10	F	12	Both hands	Pyoderma Staph. aureus CP	L hand 5% SAT, 30% U in H R hand 5% SAT in H	4 days 6 days
11	F	14	Both hands	Pyoderma Staph. aureus CP.	L hand 5% SAT, 30% U in H R hand 5% SAT in H	5 days 7 days
12	M	45	Face	Eczematoid dermatitis Staph. aureus CP.	L side 3% aq. NaSAT, wet packs R side 10% SAT, 20% L, 70% U, 1 part in 2 parts H ₂ O. Wet packs	Caustic action Rx discontinued
13	F	23	Both hands	Pyoderma Staph. aureus CP. Hem. Strep	R hand 10% SAT, 20% L, 70% U, 1 part in 2 parts H ₂ O Wet packs L hand 3% aq. NaSAT wet packs	4 5 days 7 days
14	F	24	Both hands and forearms	Eczematoid dermatitis Staph. aureus CP.	R arm 10% SAT, 20% L, 70% U, 1 part in 2 parts H ₂ O Wet packs L arm 3% aq. NaSAT wet packs	No improvement in 7 days No improvement in 7 days

TABLE 1—Continued

Case No	Sex	Age	Area Involved	Diagnosis	Treatment	Healing Time Comments
15	F	45	Both legs	Ecthyma Staph. aureus CP.	R leg 10% SAT, 20% L, 70% U, 1 part in 2 parts H ₂ O Wet packs L leg 3% aq. NaSAT, wet packs	No improvement in 6 days No improvement in 6 days
16	F	5	Face	Impetigo Staph. aureus CP.	R side 5% SAT, 30% U in H L side 5% SAT in H	4 days 6 days
17	F	11	Face	Impetigo Staph. aureus	R side 5% SAT, 30% U in H L side 5% SAT in H	4 1/2 days 6 1/2 days
18	F	15	Face	Impetigo Staph. aureus CP.	R side 5% SAT, 30% U in H L side 5% SAT in H	5 days 5 days
19	M	14	Face, both hands	Impetigo Staph. aureus CP.	L side 5% SAT, 30% U in H R side 5% SAT in H	5 1/2 days 6 days
20	F	12	Face	Impetigo Staph. aureus CP.	R side 5% SAT, 30% U in H L side 5% SAT in H	5 days 5 days
21	F	24	Both hands	Exzematoid dermatitis Hem. Strep.	R hand 10% SAT, 20% L, 70% U powder L hand SAT powder	7 days 10 days
22	F	55	Both legs	Ecthyma Staph. aureus CP.	R leg 5% SAT, 30% U in H L leg 5% SAT in H	11 days 16 days
23	M	37	Both hands and forearms	Exzematoid dermatitis Staph. aureus CP.	R arm 10% SAT, 20% L, 70% U, 1 part in 2 parts H ₂ O Wet packs L arm 3% aq. NaSAT	No improvement in 7 days No improvement in 7 days
24	M	56	Both hands	Pyoderma Hem. Strep Staph. aureus CP.	R hand 5% SAT, 30% U in H L hand 5% SAT in H	6 days 10 days
25	F	14	Face and both hands	Impetigo Staph. aureus CP.	R side 5% SAT, 30% U in H L side 5% SAT in H	5 days 7 days
26	M	16	Face and both hands	Impetigo Staph. aureus CP.	R side 5% SAT, 30% U in H L side 5% SAT in H	3 days 4 1/2 days
27	F	15	Both hands	Pyoderma Hem. Strep Staph. aureus CP.	R hand 10% SAT, 20% L, 70% U, 1 part in 2 parts H ₂ O Wet packs L hand 3% aq. NaSAT wet packs	3 1/2 day 5 1/2 days
28	F	29	Both hands	Exzematoid dermatitis Staph. aureus CP.	L hand 5% SAT, 30% U in H R hand 5% SAT in H	5 days Still active, and lesions spreading after 8 days

(Strakosch, E. A., and Clark, W. G.: *Minnesota Medicine*.)

TABLE 2—SUMMARY OF 261 PATIENTS TREATED WITH THE SULFONAMIDES IN THE DERMATOLOGIC WARDS AT BELLEVUE HOSPITAL

Disease	Number Treated	Highest Dose Gm.	Lowest Dose Gm.	Average Dose Gm.	Average No. Days Treated	Cured	Im- proved	Un- improved
Erysipelas	106	58	10	27.3	4.6	102		2 died
Lymphogranuloma venereum	43	132	17	51.0	12.6		43	
Ecthyma (L.G.V.)	2	144	66	105	27		1	1
Rectal stricture (L.G.V.)	4	Sulfaguanadine (6 Gm. four times a day 1 to 2 weeks)					3	1
Chancroid and Chancroidal bubo	32	120	24	48	12.1	32		
	2	Sulfathiazole powder in ten cases				2		
Ecthyma	9	53	16	31	8.3	15		
Oral	6	5 to 10% Sulfathiazole ointment				8.5		
Impetigo contagiosa	1					1		
Oral	9	10% Sulfathiazole ointment				6	1	2
Syccosis vulgaris and folliculitis	7	10% Sulfathiazole ointment					5	2
Folliculitis abscedens et sup- purans	1	46	8	32	8		1	
Nonspecific inguinal adenitis	2							
Nonspecific penile ulcers	7	44	20	32	8	9		
Lymphangitis associated with dermatophytosis	5	28	12	20	5	5		
Variolous ulcers	5	Sulfathiazole powder					4	1
Furunculosis	3	60	42	48	11	2		1
Carbuncle with furunculosis (Also sulfathiazole powder in wound after incision)	1	44	44	44	11	1		
Infectious dermatitis eczematoid	1						3	
Oral	2	5% Sulfathiazole ointment						
Allergic eczema with superim- posed secondary infection	3	5 to 10% Sulfathiazole ointment					3	
Dermatitis herpetiformis	4	46.5	30	37.5	15		4	
Pyoderma gangrenosum	1	Sulfathiazole powder					1	
Solid edema of ears	3	84	56	74	18		3	
		One patient received sulfanilamide Large ulcerated areas treated with powder or 10% Sulfathiazole ointment						
Pemphigus	5	(1) Oral 20					5	
Axillary adenitis	1					1		
Scabies with superimposed secondary infection	1	Sulfathiazole ointment 5 to 10%				1		
Keratoderma blennorrhagicum	1	84				21	1	
Condylomata acuminata	2	(1) Sulfathiazole powder (1) Sulfathiazole ointment					1	1
Vaccinia	1	Sulfanilamide 34				8	1	
Gonorrheal urethritis	12	68	20	49	11.6	12 or improved		
Gonorrheal cervicitis	11	34	18	24	5	11 or improved		
Lichen planus	1	44				11		1
Lupus erythematosus (disoid)	1	56				14		1
Granuloma inguinale	4	56	36	45	12			4
Pustular acne	3	5 to 10% Sulfathiazole ointment					3	
Associated syphilis	24							

(Costello, M. J.; Rubinowitz, A. M., and Landy, S. E. - N. Y. State J. M.)

these cases the skin lesions were either heavily crusted or there was an abundance of necrotic tissue and pus.

To overcome the lack of efficacy of the sulfonamides when applied locally in pustular skin lesions the authors used a powder consisting of urea 90 per cent and sulfanilamide 10 per cent.

TABLE 3—SUMMARY OF TOXIC MANIFESTATIONS IN 196 PATIENTS TREATED WITH SULFATHIAZOLE IN THE DERMATOLOGIC WARDS AT BELLEVUE HOSPITAL

Type of Manifestation	Number of Cases	Percentage of Cases	Amount of Sulfathiazole Given			Day of Occurrence		
			Lowest	Highest	Average	Lowest	Highest	Average
Thermic reaction	27	14%	17	70	35	4	17	8
Drug eruption . .	21	10	10	70	34	2	17	8
Conjunctivitis bilateral	10	5	12	96	50	3	24	12
Sulfathiazole crystals in urine		33	
Neutropenia-2 Leukopenia-1	3	1.5	32	64	53	8	16	12
Headache .	20	10				1		1-2
Nausea . .	12	6						1-2
Vomiting	8	4						1-2
Psychic disorientation	3	1.5	14	42	23		10	6
Chills .	3	1.5						
Jaundice	1		42	42	42			20
Hepatitis	1		42	42	42			20
Arthralgia	2		18	22	20			...
Pleurisy with effusion ?	1		42	42	42			20
Neuritis	1		42	42	42			20

(Costello, M. J., Rubinowitz, A. M., and Landy, S. E. *N. Y. State J. M.*)

The high percentage of urea in this mixture mechanically removes sulfonamide inhibitors present in the lesions (Marshall²) by its peptizing and hyperemic action. Also, the strong urea increases the solubility of the sulfonamides, as has been pointed out by Sobin,³ and cleans the wounds by its solvent action on necrotic tissue.

Costello, Rubinowitz, and Landy⁴ report on 261 patients treated with sulfonamide drugs in the dermatologic wards at Bellevue Hospital, New York City, 221 of the patients receiving the drugs orally. Sulfathiazole was administered in 196 cases, sulfanilamide in 8, sulfadiazine in 9, sulfaguanidine in 5, sulfapyridine in 3, 12 patients received local applications of sulfathiazole powder, 18 received sulfathiazole ointment, and 10 received sulfathiazole orally plus sulfathiazole powder or ointment locally. About 29 different dermatological conditions were treated.

TABLE 4—TYPES OF DERMATITIS FOLLOWING ORAL SULFATHIAZOLE THERAPY IN 196 PATIENTS ON THE DERMATOLOGIC WARDS AT BELLEVUE HOSPITAL

Erythema nodosum (Sulfadiazine, 1)	5
Urticaria—later becoming purpuric	3
Scarlatiform or erythematous	6
Papular	2
Papulovesicular	1
Papulopustular—acneform	1
Angioneurotic edema	3
Total	21

Associated with thermic reaction, 16 times.

(Costello, M. J., Rubinowitz, A. M., and Landy, S. E. *N. Y. State J. M.*)

Dosage: The high dosage of sulfonamides so often necessary in many diseases are seldom essential in dermatologic lesions. Usually a dosage of 1 Gm. orally four or five times a day at four-hour intervals is sufficient. However, in cases of severe infection, one should give an initial large dose and then continue the drug at a sufficient dosage to maintain a high blood level.

Scope of Sulfonamide Therapy in Dermatology

Brunsting⁵ gives the following information on sulfonamide therapy in dermatology:

Erysipelas, Cellulitis, Lymphangitis, and Erysipeloid: It is generally agreed that these drugs are of distinct value in the treatment of erysipelas. When the infection is localized, roentgen therapy alone is adequate; in cases in which the patients are infants and young children, ultraviolet irradiation is employed. In extensive erysipelas, if the patient is a debilitated or elderly person and the prognosis is naturally guarded, we prefer to combine roentgen therapy and chemotherapy.

Localized streptococcic infections, such as cellulitis and lymphangitis, are favorably influenced by vigorous therapy with sulfanilamide or sulfathiazole. Lymphangitis of the legs is not infrequently a sequel to dermatophytosis of the feet, and in such cases the use of the sulfonamide drugs is helpful in the control of the

febrile episode. In cases of recurrent regional lymphangitis of the face, ears, genitalia, and extremities, in which lymphedema develops frequently after repeated attacks, we have confirmed Mercer's observation that these drugs shorten the period of recovery and, in some instances, interrupt the cycle of recurrences.

Sulfanilamide has been used successfully in the treatment of erysipeloid of Rosenbach, an occupational infection of the hands of butchers and other handlers of meat and fish.

Pemphigus: The test of true pemphigus is its fatal termination. The prognosis has not been changed by the introduction of sulfanilamide and its derivatives. There are borderline cases in which the involvement is limited to the eyes and mouth, and other cases in which the disease eventually proves to be erythema multiforme or dermatitis herpetiformis. It probably is in this group that the administration of these drugs occasionally proves beneficial. Lynch reported favorably on the influence of sulfathiazole in benign familial pemphigus. We have administered intensive doses of various sulfonamide drugs in four cases of pemphigus vulgaris the past two years. Two of the patients are dead and the others are failing rapidly. In two cases of pemphigus vegetans we noted that the affected sites were cleared by a combination of local and systemic treatment, but there was a gradual recurrence despite intermittent therapy.

Lupus Erythematosus: There are conflicting reports as to the value of these drugs in cases of lupus erythematosus. In the treatment of the discoid type, Barber noted a peculiar febrile reaction after the administration of small doses of sulfanilamide. He observed a focal flare of the lesions and a surprising degree of improvement under continued treatment. Other reports have been less optimistic. Our experience with this treatment in cases of discoid lupus erythematosus is limited, but we have not noted any benefit.

Disseminated lupus erythematosus is invariably a disease of grave prognosis and there is little evidence to show that its ultimate course can be affected by the available sulfonamide compounds. There are reports of clinical improvement and even of

prolonged remission under such treatment, but, for the most part, these concern the disseminated discoid phase of the disease. There is no fixed line of distinction between the acute and subacute stages of disseminated lupus erythematosus. An outstanding characteristic of both conditions is the extreme degree of reactivity of the patient to minor trauma and operation, infections, sunlight, blood transfusions, and medicaments. In the past three years, seven of our patients, two men and five women, received sulfanilamide and allied compounds in the course of treatment of subacute disseminated lupus erythematosus. There was no benefit that could be ascribed to the drugs and four of the women have since died. There was an unusually high incidence of untoward reactions to the treatment. Cutaneous lesions flared and became widespread in one case; ulcerative stomatitis and vulvitis appeared in another. In a third case vomiting and transient jaundice occurred. In another case, increased anemia and leukopenia developed and edema of the ankles and oliguria were observed. Finally, in a case in which the disease was in the acute phase, gross hematuria developed after sulfapyridine had been administered for four days for a complicating terminal pneumonia. An accumulation of such experience tends to promote an attitude of conservatism and a respect for the disease. Some believe that there is sufficient merit in the treatment to warrant further trial. Perhaps the use of sulfadiazine, which is relatively nontoxic, can be applied with caution in selected cases.

Pyoderma Gangrenosum: In chronic ulcerative colitis there is invariably a marked degree of debility and, therefore, supportive measures, such as blood transfusions, supplementary vitamins, vaccines, and arsenic, usually are indicated. In addition, in selected cases appreciable benefit results from the judicious use of azosulfamide or sulfaguanidine, the two drugs that are best tolerated in this disease. We used this treatment in 12 cases in which pyoderma gangrenosum occurred as a complication of chronic ulcerative colitis. In two cases the cutaneous lesions were in the vegetative stage; in the other cases there was one or more typical boggy ulcers of the skin. As a rule, the

response of the cutaneous lesions runs parallel to the degree of activity of the colitis and the general health. In six cases we noted beneficial results that could be attributed to the sulfonamide drugs; in four cases the effects were slow and irregular; in two cases, after temporary improvement, there was a decline in general health and the administration of the drugs was discontinued because of indigestion. Weiner reported remarkable response to prolonged sulfanilamide therapy in one case of extensive pyoderma gangrenosum and colitis. Likewise, Cipollaro observed benefit from sulfanilamide in a case in which similar lesions followed mastoiditis and cellulitis of the cheek.

Hidradenitis Suppurativa: This condition is commoner than is generally appreciated. It is essentially a form of pyoderma with predilection for certain regions of the body, the axillae or genitalia, where apocrine glands are abundant and active. Lesions may appear as deep seated furuncles or as irregular, nodular abscesses with communicating fistulous tracts. I believe that dissecting cellulitis of the scalp is a part of the process. Frequently in the same case there is involvement of the scalp, axillae, inguinal folds, pubis, genitalia, perineum, and the perianal region, and there also may be signs of deep-seated acne of the face, nuchal region, and trunk. In many cases the patients are obese and have an oily skin. There may be multiple cystic abscesses of the lower half of the breasts if the patient is a woman. Cellulitis and lymphangitis with ulceration and systemic reaction are not uncommon.

The treatment of hidradenitis suppurativa consists of a combination of suitable diet, scrupulous local hygiene, drainage of abscesses, and removal of comedones, roentgen therapy, surgical excision of localized plaques of infection, and the administration of sulfanilamide, sulfathiazole, or sulfadiazine in sizable doses in repeated courses according to indications. The sulfonamide drugs are of particular value when used locally and systemically in cases of progressive ulceration and inflammatory reaction and in cases of dissecting cellulitis of the scalp.

Keratoderma Blennorrhagicum: Sulfathiazole is the drug of choice in the treatment of gonorrhea. In the rare instances in which crusted keratoderma and polyarthrititis are associated, the use of the drug alone is not sufficient. I agree with Combes that the concurrent use of fever therapy in such cases is an indispensable aid to recovery. In two cases in which keratoderma blennorrhagicum was associated with extensive destructive polyarthrititis and pronounced debility, fever therapy and the prolonged administration of large doses of sulfathiazole proved beneficial. In both instances additional supportive measures were needed during the long period of hospital care.

Dermatomyositis: Sulfanilamide was administered, in the course of other treatment, in four cases of dermatomyositis. There was no improvement that could be attributed to the drug, but a further trial is indicated, especially in the early stages of the disease.

Erythema Nodosum: Sulfanilamide and azosulfamide were given in adequate doses to four patients who had erythema nodosum, but no benefit was produced.

Erythema Multiforme: In four cases of this condition we have observed an irregular response to treatment with sulfanilamide. Recurrences are not prevented, but when the drug is administered at the onset of symptoms the clinical course seems to be shortened. In one case the drug did not produce any benefit. In another case, in which the patient was a woman, aged 23 years, who had had four recurrent attacks in the preceding two years, we noted a favorable response to treatment during an acute attack. Following this, several infected teeth were removed and, with one slight exception, there has been no recurrence in 28 months. The cause of recurrent erythema multiforme bullosum is obscure. After a thorough search for suspicious foci of infection, cautious use of sulfonamide treatment seems warranted empirically.

Dermatitis Herpetiformis: Any contribution to the control of this erratic and stubborn disorder is more than welcome. Surprising benefit has been reported in a few cases of chronic der-

matitis herpetiformis by the administration of sulfapyridine. Costello observed one case in which the disease remained in remission for many months after treatment with sulfapyridine, and Cornbleet and Rattner reported two cases in which such treatment proved beneficial.

During the past two years we have administered sulfapyridine empirically in a series of cases of dermatitis herpetiformis and can attest the brilliant therapeutic effect of the drug almost without exception, but, unfortunately, the results are not permanent and the benefits subside soon after the drug is eliminated from the system. In moderate dosage, beginning with 2 to 3 Gm. daily for three or four days, then 1 Gm. daily for a week, and then of 1 Gm. daily intermittently, the drug is well tolerated and we have observed no untoward reactions. One patient was a child, aged three years, with symptoms of four months' duration. The others were adults with chronic dermatitis herpetiformis, some of them with signs of arsenism. In a few instances it has been possible to use the administration of sulfapyridine as a therapeutic test in eliminating the possibility of dermatitis herpetiformis where the clinical picture presented the confusing combination of this disease with erythema multiforme and pemphigus. Sulfapyridine penetrates the nervous system to a greater degree than do the other sulfonamide preparations, but there is no rational explanation for its apparent specific palliative action in dermatitis herpetiformis. If treatment with this drug is to be carried out intermittently over a period of time, the patient should be under close observation and the blood and urine should be examined frequently. Sulfanilamide is sometimes useful, but it appears to be of less value than sulfapyridine in dermatitis herpetiformis.

In one case of long-standing urticaria perstans, in which the patient was a young woman, and in which the configuration of the lesions at times resembled that of dermatitis herpetiformis, complete relief followed the use of sulfaguanidine after the other sulfonamide drugs had been tried without benefit.

Pyoderma, Furuncle, and Carbuncle: We have not felt justified in the use of sulfanilamide systemically in cases of solitary abscesses or furuncles, but, occasionally, in the presence of large carbuncles the oral administration of the sulfonamide drugs and the local application of powdered sulfathiazole to open wounds have produced considerable benefit. In cases of extensive furunculosis, especially in the presence of diabetes, such treatment is worthy of consideration.

Certain pyogenic burrowing ulcers are benefited by the oral administration of sulfanilamide or sulfathiazole, and the local implantation alternately of powdered sulfathiazole and zinc peroxide.

Pyogenic Dermatitis: In some instances of extensive, incapacitating infectious dermatosis, the pyogenic element can often be controlled by the judicious combination of internal and topical therapy with sulfanilamide and sulfathiazole. In cases in which the affection is localized it is best to use topical measures alone. Our results in the treatment of recalcitrant pustular eruptions of the hands and feet have been disappointing. In the rare acrodermatitis of Hallopeau, preliminary reports indicate that such treatment should be given a thorough trial.

Impetigo Contagiosa: Peterkin and Jones⁶ state that the effect of local sulfanilamide and sulfapyridine therapy in impetigo is sometimes striking but often disappointing. Sulfathiazole is the drug of choice. The writers used the drug in a water miscible cream or a starch and zinc oxide paste. Results obtained with a five per cent concentration were better than those with 2.5 per cent and compared favorably with results from ten per cent concentration.

Harris⁷ used a new physical form of sulfathiazole, a 20 per cent suspension of microcrystalline sulfathiazole. The author reports that a single application of this new physical form of sulfathiazole cured the lesions within a day and stopped the spread of the disease.

Pijon *et al.*⁸ used a water-soluble plastic (methylcellulose, methocel) and sulfadiazine preparations for bacteriostatic plastic

films in impetigo. After cleansing the scabs with cotton soaked in hydrogen peroxide, as much as possible was removed without unnecessary trauma to the infected skin area. Tincture of sulfadiazine-methocel (solution I) was then applied with a cotton applicator while the surface was still moist. This may be repeated several times until the entire area is thoroughly impregnated. Next sulfadiazine-methocel jelly (solution II) was applied to the entire area to make a coating 0.5 mm. in thickness. This will dry within three to five minutes and form a new film over the lesion. As a rule, one treatment is sufficient. The débridement should be done cautiously, since trauma might induce scar formation with possible disfigurement, but the more completely it is done the more satisfactory are the results.

Skin Reactions to Sulfonamide

Shaffer, Lentz, and McGuire⁹ point out that sulfathiazole as a local application is capable of causing cutaneous sensitization, which sensitization may manifest itself as a local contact type dermatitis with or without a disseminate eruption, or it may appear as a local or generalized exacerbation of the dermatitis for which that patient is being treated. Sulfathiazole sensitization induced by local cutaneous application may at times be elicited by oral administration of the drug. The original local sensitizing exposure to the sulfathiazole may or may not have resulted in local dermatitis. The eruption precipitated by the ingestion of sulfathiazole tends to begin and to be most severe at the sites where the sulfathiazole is applied locally, although it may later disseminate widely. Here again it may mimic the eruption for which the patient is being treated. It seems likely that pronounced pyogenic sensitivity, especially to the staphylococcus, is important as a predisposing factor in many of these eruptions.

The authors cite the following four cases of sulfathiazole dermatitis:

CASE 1: E. H., a housewife aged 28, white, on November 5, 1941, presented on the right hand a chronic, scaling, fissured and

patchy dermatitis localized to the palm and thenar eminence, and also an acute vesiculopapular dermatitis on the paronychia regions of several fingers. This condition had been present recurrently since an attack of "athlete's foot" four and one-half years before.

Appropriate clinical, laboratory, allergic, and roentgenologic studies revealed no abnormalities or evidence of foci of infection. Scrapings and cultures for fungi were negative. Several bacteriologic studies of the skin showed consistently pure cultures of hemolytic *Staphylococcus aureus*.

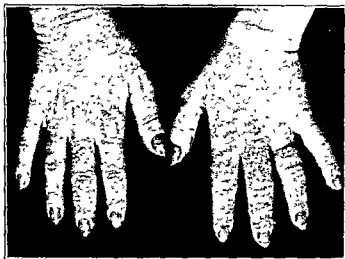


Fig. 1—Case 1. Acute dermatitis precipitated by the ingestion of sulfathiazole; primary sensitization appeared as an exacerbation of the patient's original eruption due to sulfathiazole.

(Shaffer, Lentz, and McGuire. *J. A. M. A.*)

For three weekly intervals the patient was treated with x-rays (63 roentgens), sulfathiazole five per cent in cholesterinated petrolatum and staphylococcus ambotoxoid. The latter was injected intracutaneously in a dosage of 0.1 cc. of a 1:10 dilution. This resulted in tuberculin type reactions averaging 5 by 5 cm.

On the second week the eruption was a little worse, but when observed after the third week the process had become very acute and involved the left hand as well as the wrist on the right side.

All active treatment was stopped. The eruption showed gradual improvement, so that after two months (January 27, 1942) it finally subsided to its original degree of activity.

Subsequent attempts to desensitize the patient to ambotoxoid in dilutions of 1:1000 and later of 1:10,000 were each followed by increased activity of the process. After it was determined finally that a dilution of 1:20,000 could be well tolerated, increasing concentrations were injected. When the dilution of 1:2500 was reached, however, a flare-up in the eruption appeared, so that after two such attempts ambotoxoid therapy was stopped permanently.

One week later sulfathiazole was prescribed for oral administration in a dosage of 1 Gm. every six hours. After the first dose the patient noticed stinging, burning, increased redness, tenderness, and swelling of both hands. Following a second dose the condition became greatly aggravated (Fig. 1). At the end of 12 hours an intensely pruritic and widespread papular and urticarial eruption had appeared on the face, neck, and upper extremities. Three days later the disseminate eruption had disappeared, but it took six weeks (May 5) for the local process on the hands to subside. Mistaking the sulfathiazole ointment for another preparation, the patient applied this salve to her hands on May 5. Within 24 hours an explosive generalized eruption developed resembling, but much more severe than, the condition following the oral sulfathiazole. Approximately 40 per cent of the scalp hair was lost and vesicular and bullous lesions were present on the hands and feet. The eruption subsided only after four months of palliative treatment.

CASE 2: W. W., a Negro youth aged 21, was treated recurrently from August 2, 1938, to September 3, 1940, for a relapsing, crusted, oozing, purulent eruption involving the scalp and ears. This condition was diagnosed as staphylococcal and repeated studies showed pure cultures of hemolytic *Staphylococcus aureus*.

On September 14, 1940, he was admitted to the University Hospital because a widespread vesiculopurulent eruption had developed. One week later he was given sulfanilamide orally

(2.6 Gm. a day for six days). Because of inadequate response, sulfathiazole was then administered. After eight days on a dosage of 3 Gm. a day the eruption disappeared completely.

On October 24, three days after an initial injection of staphylococcus ambotoxoid, a violent vesiculopustular eruption appeared on the bearded region, scalp and ears. With high dilu-



Fig. 2—Case 2. Pemphigoid eruption following the oral administration of a single tablet (0.5 Gm.) of sulfathiazole. The patient's original allergic response to the drug followed its local application.

(Shaffer, Lentz, and McGuire *J. A. M. A.*)

tions of the ambotoxoid attempts were made to desensitize the patient but with no beneficial effect.

On December 13 he was given an ointment containing one per cent sulfathiazole. The eruption became aggravated almost immediately, and within three days a generalized vesiculopustular and bullous eruption was present. As the basis of this eruption was not recognized and also because of his satisfactory response to sulfathiazole orally on his previous admission, this

drug was again administered on January 6, 1941, in a dosage of 0.5 Gm. every six hours. That day his temperature rose to 102.6° F. Four days later he complained of acute colicky pains in the upper part of the abdomen and nausea. Sulfathiazole was stopped. The symptoms disappeared within 24 hours and the temperature fell to normal the next day. The eruption slowly, over a period of three weeks, disappeared (February 3).

Because some activity was noted on the scalp a few days later he was given an ointment containing five per cent sulfathiazole. Again the process flared up and became more extensive.

On September 14 the patient visited a private physician, who gave him some sulfathiazole tablets. The abdominal symptoms, the rise of temperature, and the generalized bullous eruption recurred within 24 hours. For a period of three months he was treated at another hospital before recovery ensued.

On August 7, 1942, he was admitted to the University Hospital because a fairly widespread vesiculopurulent eruption had again developed.

The next day he was given a single tablet (0.5 Gm.) of sulfathiazole orally. Within one-half hour his temperature rose to 103° F., the abdominal pains appeared, and a generalized papular and urticarial eruption was present. Twenty-four hours later many of these lesions had become bullous and hemorrhagic (Fig. 2), and conjunctivitis, erosive stomatitis, gingivitis, and pharyngitis were present. After one week improvement began. Four months later the eruption had disappeared and the patient was discharged. Repeated cultures of the lesions with rare exceptions were reported as pure growths of hemolytic *Staphylococcus aureus*.

CASE 3: J. D., a white man aged 27, had an eruption on the hands in September, 1927. This recurred in 1939. He presented himself to the clinic of the department of dermatology and syphilology on May 18, 1942, because two weeks previously the process had flared up once more, this time involving also the forearms.

Examination revealed an acute, diffuse, weeping dermatitis on the sites mentioned. This was diagnosed as contact dermatitis with secondary pyogenic infection. Treatment was started with an ointment consisting of sulfathiazole six per cent, ichthammol three per cent in zinc oxide ointment.



Fig. 3—Case 3. Widely disseminate eruption evoked by oral sulfathiazole medication. This eruption appeared five days after the original contact with sulfathiazole in the form of an ointment.

(Shaffer, Lentz, and McGuire: *J. A. M. A.*)

No improvement was noted two days later. Sulfathiazole orally, 1 Gm. every six hours, was prescribed and he was given an intracutaneous injection of staphylococcus ambotoxoid 0.1 cc. of a 1:1000 dilution. A few hours after the first dose of sulfa-

thiazole the eruption became somewhat more active. After three days of this medication it had become generally disseminated (Fig. 3) and was associated with conjunctivitis and a temperature of 101.4° F.

Sulfathiazole was stopped. Two days later improvement began and within two weeks he was well (June 10).

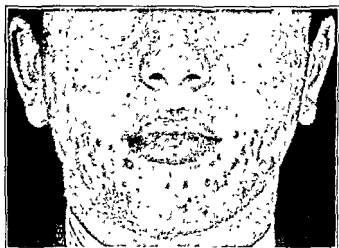


Fig. 4—Case 4. Pustular exacerbation of acne vulgaris following oral sulfathiazole medication. The acneform flare-up appeared only at the sites at which a sulfathiazole lotion had been applied previously.

(Shaffer, Lentz, and McGuire. *J A M A*)

CASE 4: C. G., a white boy aged 16, on April 30, 1942, complained of a pustular type of acne vulgaris involving the face, back, and upper part of the chest. He was treated over these regions by means of x-rays (50 roentgens, unfiltered, 85 kv. peak, 5 mm., anode-skin distance 12 inches) at intervals of 7 to 14 days. By September 30 he had received a total of 750 roentgens and the eruption had disappeared almost entirely. Local medication had consisted only of a lotion containing sulfathiazole three per cent, and sulfur three per cent, which he applied to his face but not to the remainder of the eruption, by means of a moistened piece of cotton held in either hand.

Six weeks after the use of the lotion was begun a dermatitis appeared on the face and hands. He stopped using the lotion, and the eruption disappeared within one week. Several days later he again applied the preparation, and a prompt recurrence of the dermatitis followed. Following subsidence of this condition the same lotion was prescribed, but with the omission of the sulfathiazole. He was able to use this preparation without ill effect.



(Volini, J. E.; Levitt, R. O., and O'Neil, H. B.: "Cutaneous and Conjunctival Manifestations of Sulfathiazole Intoxication," *J. A. M. A.*)

Fig. 5—Nodular rash with purpuric base.

On October 7 the patient's home physician prescribed sulfathiazole tablets for oral administration because the patient complained of a sore throat. Within 24 hours, after he had taken four tablets, acute redness and swelling of the face developed. This was accompanied by a prompt and pronounced pustular exacerbation of the acne on the face only. The other sites of the preëxisting acne were not affected. The temperature rose to 101° F., but dropped to normal the next day after the drug had been discontinued. Five days later the dermatitis was about 50 per cent better and the acneiform flare-up had begun to subside (Fig. 4).

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CHEMOTHERAPY IN DIABETES MELLITUS

Diabetic acidosis has been reported on several occasions as a complication of chemotherapy in diabetic patients. Southworth¹ reported on acidosis associated with the administration of pronylin. Beardwood and Rouse² attributed three cases of diabetic acidosis to the administration of sulfanilamide. Lest this might make the physician hesitant to prescribe the sulfonamides to diabetic patients, it is interesting to note that Styron *et al.*³ report the use of sulfadiazine and sulfathiazole in more than 100 diabetic patients for various infections in a period of one year without encountering the complication of acidosis. The patients ranged in age from 7 to 86 years and the duration of the diabetes from 1 month to 33 years.

TABLE 1—RESULTS OF TREATMENT OF 100 DIABETIC PATIENTS WITH SULFADIAZINE AND SULFATHIAZOLE

Diagnosis	Number	Improved
Foot infection	52	49
Cystitis or pyelonephritis	20	18
Pneumonia	15	13
Carbuncle	4	4
Infected finger	3	1 saved, 2 amputations
Suppurative adenitis	3	3
Miscellaneous	14	13
Total diagnoses	111	103

Deaths.

4 (3 among 26 amputations of the leg)
(Styron, C. W., *et al.*, J. A. M. A.)

"It seems evident," say these authors, "that one cannot expect chemotherapy to cure necrotic lesions such as carbuncles and gangrene in the diabetic. However, it seems to control extension of pyogenic infections and to have special advantages in pneumonia and particularly in genitourinary infections, to which the diabetic are notoriously vulnerable."

Foot infections were given an initial dose of 3 Gm. (45 grains) of either drug and maintained with 1 Gm. (15 grains) every four to six hours. The average blood level was 6.3 mg. per 100 cc.

Urinary infections received smaller dosage given over longer periods. A frequent procedure was to give 1 Gm. (15 grains)

TABLE 2—CHEMOTHERAPY IN 52 DIABETIC FOOT INFECTIONS

	<i>Dorsalis Pedis Pulsation</i>			
	<i>Palpable</i>		<i>Nonpalpable</i>	
	<i>Number</i>	<i>Per cent</i>	<i>Number</i>	<i>Per cent</i>
Cases . . .	20	39	32	61
Major amputation	3	15	23	72
Successful local amputation or drainage	17	85	7	22
Amputation refused.	0	0	1*	3
Amputation planned.	0	0	1*	3
Deaths.	0	0	3	9

*Patients died.

(Styron, C. W., *et al.*: *J. A. M. A.*)

TABLE 3—EFFECT OF CHEMOTHERAPY ON INSULIN DOSAGE IN 100 DIABETIC PATIENTS

1. Insulin increased		45
2. Insulin decreased	14	..
Insulin remained the same	24	
Insulin equal to or less than discharge dose .	17	55

Pneumonia patients in the above series were usually given an initial dose of two or three Gm. (30 or 45 grains) of sulfadiazine or sulfathiazole followed by one Gm. every four to six hours until the temperature remained normal for 24 to 48 hours. The average blood level of the drug was five mg. per 100 cc.

(Styron, C. W., *et al.*: *J. A. M. A.*)

every four to six hours for the first 24 hours and then reduce the dosage to 0.25 to 0.5 Gm. ($3\frac{3}{4}$ to $7\frac{1}{2}$ grains) every four hours. Blood levels averaged 3.5 mg. per 100 cc.

Toxic symptoms in the diabetic patients appeared with about the same frequency as in nondiabetic patients.

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DIARRHEA

See page 128



DIPHTHERIA

See page 130



BACILLARY DYSENTERY

Yannet, Leibovitz, and Deutsch,¹ reporting on an epidemic of Sonne dysentery, present a comparison between a group receiving sulfathiazole and a group not receiving chemotherapy. The average age of the former group was about 11 years, while of the latter it was about 14 years. Statistically this difference was of no significance. The dose of sulfathiazole varied between 3 and 6 Gm. a day, depending on the weight of the patient, and was given in four to six doses a day for an average of four days. No evidence of toxicity due to the administration of the drug was encountered. As noted by others, the average number of days of fever and diarrhea was less in the drug-treated group, although the differences were small owing to the mildness of the disease. When only the cases of more than average severity were compared in the two groups, however, the beneficial effects of sulfathiazole were more apparent. The clinical picture rapidly

improved, while the duration of fever and diarrhea was definitely decreased.

The study of the weekly stool cultures in both groups was of considerable interest. In the control group, the average number of days from the onset of illness until the rectal cultures were consistently negative was 19.7 ± 3.7 (standard error) with a range from 4 to 48 days. In the sulfathiazole-treated group, the number of days from the cessation of therapy until the rectal cultures became negative average 33.9 ± 4.4 (standard error) with a range from 7 to 84 days.

Stool cultures during the administration of sulfathiazole, and for some days immediately thereafter, showed either no growth or an occasional colony of *Escherichia coli* on MacConkey's plates. However, in 20 of the 27 patients treated with the drug there was a return of the dysentery organisms within three weeks after treatment was stopped. Actually, seven cases became positive during the first week, ten additional cases during the second week, and three during the third week. There were no relapses in the group not receiving sulfathiazole, while relapses occurred at varying intervals in three cases following the cessation of therapy in the drug-treated group. One of the cases is of particular interest. This was a 12-year-old boy, who was admitted to the hospital on December 19, soon after the development of fever and diarrhea. Sulfathiazole was started on admission and continued for four days. The temperature and number of stools became normal within 24 hours after the drug was started, and the patient was returned to his cottage two days after the cessation of drug therapy. At this point rectal cultures showed no bacterial growth. Two days later his temperature rose to 102°F . and numerous diarrheal stools were passed that were positive for *Bacterium sonnei*. Another four-day course of sulfathiazole was administered and a rapid clinical recovery followed. Again *the rectal culture showed no growth. One week later, however,* the Sonne organism was again isolated. On January 7, 1942, almost three weeks after his initial attack, he had, for the third time, diarrhea, fever, and vomiting. He received no drug

TABLE I—COMPARISON OF CONTROL AND SULFATHIAZOLE TREATED GROUPS

Group	Number	Average Age, Years	Duration of Fever, Days*	Duration of Diarrhea, Days	First Negative Culture, Day
Control . . .	17	13.8 \pm 2.6†	1.3 \pm 0.2	2.9 \pm 0.4	19.7 \pm 3.7
Sulfathiazole treated	27	11.0 \pm 1.3	1.0 \pm 0.1	1.5 \pm 0.2	33.9 \pm 4.4

* 100° F. or higher.

† Standard error.
(Yannet, H., et al.: J. A. M. A.)

therapy during this attack and was clinically well within 48 hours. Cultures taken at weekly intervals following this relapse remained negative. In the other two cases the relapses occurred 5 and 11 days, respectively, after the cessation of drug therapy. Rectal cultures, which had shown no growth or only coliform bacilli following the cessation of drug therapy, again became positive for the Sonne organism. Additional drug therapy was not given and both patients made an uneventful recovery. In both cases rectal cultures became consistently negative 14 days after their respective relapses.

During the study of healthy contacts in the institution, as well as the new admissions, 13 carriers of *Bacterium sonnei* were discovered. Ten of these harbored the epidemic strain, while three (the new admissions from the community) harbored a strain which differed from the epidemic strain by being rapid rhamnose fermenters.

Six of the carriers were treated with 3 Gm. of sulfaguanidine a day for seven days, therapy being instituted within 48 hours after the first positive culture had been obtained. All but one remained well and failed on subsequent weekly cultures to show the dysentery organism, although they were followed for several months. The six, a carrier of the epidemic strain, received the usual dose of sulfaguanidine for seven days. Rectal cultures taken on the last day of therapy showed no bacterial growth on MacConkey's medium. Five days after the cessation of drug

therapy, the clinical picture of dysentery developed with fever, diarrhea, and vomiting. A rectal culture at this time was positive for the Sonne organism. He was treated with sulfathiazole and recovered clinically in 48 hours. Rectal cultures, however, remained positive for almost two months. This case is included with the sulfathiazole-treated group.

That the sulfaguanidine contributed significantly to the clearing of the carrier state is doubtful in our cases, because of the essentially similar course followed by the group of carriers that received no drug therapy. Of the seven subjects in this group, six failed to show subsequent positive cultures after the organism was initially discovered, although rectal cultures were performed for almost two months. The seventh had consistently positive stool cultures for five weeks. At the end of this period he was given a similar course of sulfaguanidine. Subsequent positive cultures were not found following therapy.

The interesting feature of this phase of the study is the frequent occurrence of relatively short periods during which healthy carriers may harbor the dysentery organisms and thus serve as potential sources for the spread of the disease if not isolated. That the epidemic was spread in the institution by means of temporary carrier states in the relief personnel is not unlikely. Whether the prolonged carrier states would be benefited by sulfaguanidine remains to be seen. A recent study by Rantz and Kirby suggests that this may be the case. In that study, however, the organism isolated was identified as *Shigella alkalescens*.

Rubens and his associates² used sulfathiazole in the treatment of 17 children, who entered the Cook County Children's Hospital because of frequent watery stools containing blood and mucus. There were 29 control children. Sulfathiazole was started from two to four days after the patients' hospitalization and continued until the stools were normal in number, color, and consistency, and until the cultures of three weekly consecutive stools were negative. The average daily dose of the drug was 0.1 Gm. (1½ grains) per pound of body weight, given in

six equal doses at intervals of four hours. Nonspecific, supportive therapeutic measures, as indicated by the clinical condition, were employed. The eight patients with clinical dysentery from whose stools positive cultures of *Bacterium dysenteriae* and *Salmonella* were obtained responded better to sulfathiazole than the nine clinically identical patients whose stool cultures were

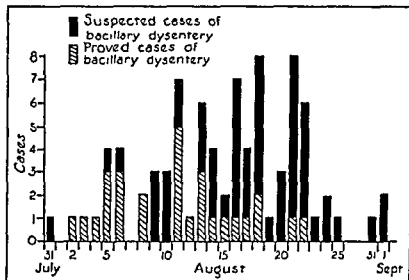


Chart 1.—The distribution of cases by date of onset, indicating occurrence of suspected and proved cases.

(Smyth, C. J., et al. / J. A. M. A.)

negative. The ratio of the duration of disease after treatment was started is 2.9 to 4.7 days. The duration of diarrhea was shorter in the eight patients after sulfathiazole was started than it was in the 13 similar patients treated identically but without sulfathiazole. The ratio of days of diarrhea after sulfathiazole was started was 2.9 to 8.8. Therefore, sulfathiazole appeared to have definite value in the treatment of patients whose stool cultures were positive for dysentery or *Salmonella* organisms, but no statistically significant effect was demonstrable in those whose stools were negative for the organisms.

ceived another course of sulfaguanidine and then their stools became negative again. This indicates the necessity for continued check of the stools for several weeks after they become negative for the infective organism.

Smyth *et al.*⁵ also report on the use of sulfaguanidine and succinylsulfathiazole in acute bacillary dysentery (Flexner), with the following conclusions: It is evident from this study of 28 cases that both sulfaguanidine and succinylsulfathiazole are of distinct value in the treatment of acute bacillary dysentery (Flexner). It must be emphasized, however, that failures have occurred following the use of each of these drugs. Because suc-

TABLE 2—TOTAL DOSAGE AND CORRESPONDING BLOOD CONCENTRATIONS OF SULLAGUANIDINE IN 12 CASES

Patient	Weight, kg	Total Dose in Grams to Date	Blood Concentration of Drug, mg per 100 cc
T. T	81.8	48.5	1.0
		78.5	2.2
J. S	60.9	15.0	3.2
		81.0	10.0
		103.0	7.2
C. K	71.4	28.0	7.7
G. R	48	32.0	4.2
		53.0	5.6
		68.0	6.2
		104.5	8.3
J. F	51.8	48.0	0.9
		72.0	1.5
M. N	60	36.0	2.1
W. S	81.8	54.0	5.0
F. K	54.1	45.0	3.2
R. G	56.4	27.5	16.6
		57.5	4.6
J. T	43.2	41.0	4.3
J. P	68	25.0	4.5
		85.0	5.3
R. H	75.5	72.0	3.6
		120.0	14.3

(Smyth, C. J., *et al.* J. A. M. A.)

TABLE 3—TOTAL DOSAGE AND CORRESPONDING BLOOD CONCENTRATIONS OF SUCCINYLSULFATHIAZOLE IN 24 CASES

Patient	Weight, kg.	Total Dose in Grams to Date	Blood Concentration of Drug, mg. per 100 cc.	
			Free	Total
M. S.	50.8	34.0	0.87	0.89
		58.0	0.35	0.41
		78.0	0.25	0.5
J. B.	65.9	64.0	0.77	1.12
		100.0	0.41	0.51
		122.0	0.23	0.25
J. F.	51.8	15.0	0.92	1.0
A. S.	48.7	104.0	0.73	1.07
		144.0	0.66	0.81
		168.0	0.53	0.57
J. P. B. . . .	56.8	50.0	0.61	0.82
		80.0	1.0	1.08
		101.0	0.19	0.5
F. K.	54.1	87.5	0.97	0.99
		145.0	0.33	0.5
P. L.	62.3	27.5	1.39	1.45
		57.5	0.33	0.46
D. P.	63.6	57.0	0.40	0.45
		159.0	0.50	1.10
		219.0	1.0	1.39
G. W.	61.4	16.5	0.19	0.19
		43.5	0.3	0.46
M. S.	65.5	81.0	0.38	0.40
W. H.	50	37.0	0.21	0.37
G. G.	77.7	25.0	0.29	0.41
S. D.	60.9	18.0	0.1	0.17
		30.0	0.49	0.54
		48.0	0.69	0.27
		60.0	0.50	0.48
S. S.	99.1	70.5	0.20	0.18
		118.5	0.70	0.68
		166.5	0.20	0.46
			0.28	0.25
J. A.	56.8	24.0	0.39	0.41
		48.0	0.42	0.45
		68.0	0.46	0.91
W. B.	59.5	115.0	0.82	0.86
J. K.	62.3	39.0	0.31	0.32
P. McM. . . .	67.3	42.5	0.32	0.34
R. N.	73.6	63.0	0.25	0.27
A. G.	45	41.0	0.64	0.65
H. S.	60.5	49.0	0.08	0.11
		75.0	0.38	0.41
A. T.	75.9	40.0	0.2	0.31
		76.0	0.6	0.74
J. R.	73	98.0	0.4	0.6
E. S.	52.3	48	0.87	0.63
		84	0.58	0.57

(Smyth, C. J., et al.: *J. A. M. A.*)

cinylsulfathiazole is equally effective, and because it is without the potential toxic effects of sulfaguanidine, we believe that it is the drug of choice in the treatment of acute bacillary dysentery (Flexner).

We consider that succinylsulfathiazole given in doses of 0.25 Gm. per kg. initially and 0.25 Gm. per kg. daily for at least six consecutive days was adequate to effect a cure in 12 of 14, or 85 per cent, of our cases. We observed that doses of twice this amount may be administered without untoward reactions, and it is suggested that if fever and diarrhea are not controlled after three days of therapy with the smaller doses twice the amount of the original dose be given.

We wish to stress the importance of repeated stool cultures for at least three weeks after therapy has been discontinued. Although the final decision regarding the value of succinylsulfathiazole will require further clinical use, the results of this comparative study indicate that it is a definite advance in the treatment of this important enteric disease, and may prove to be of great value in the treatment of other types of bacillary dysentery.

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EMPHYEMA

In an article on the influence of sulfonamide therapy on post-pneumonic empyema thoracis, Burford and Blades¹ state that it is their belief that once the pneumonia has been adequately controlled, and certainly when pus has been demonstrated in

the pleural cavity, sulfonamide therapy should be discontinued. To treat the empyema, once it has developed, chemotherapeutically is not only irrational but may be definitely deleterious. Such a course will only obscure the picture and render the proper surgical procedure more difficult. The idea, unfortunately, too common among pediatricians and internists, that a purulent pleurisy caused by organisms affected by the sulfonamide drugs, once formed will often take care of itself if chemotherapy is continued, is just as fallacious as assuming that any other abscess will do the same without proper surgical drainage.

Two of the most valuable clinical guideposts in the proper treatment of empyema are the fever curve and the patient's appetite. In the case in which drainage has been adequate the temperature returns quite promptly to normal and the appetite becomes good and even voracious. Conversely, when for one reason or another the drainage becomes inadequate, there is a prompt rise in temperature and an associate anorexia. The sulfonamides are notorious for their antipyretic properties and for their anorexic effects. The patient with a drained empyema who is being treated by one of these drugs often provides a confusing dilemma. One is lulled into a false sense of security by the antipyretic effect of the drug on the one hand and alarmed by its appetite-destroying properties on the other.

Also see page 130.

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PNEUMOCOCCIC ENDOCARDITIS

(Also see page 130)

Pneumococcic endocarditis is a highly fatal disease, but Blumberg, Heine, and Lipshutz¹ report the cure of a case treated with sulfonamides.

The patient was first seen on December 1, 1941, during a severe chill. The only positive conditions on physical examina-

tion were a loud harsh blowing systolic murmur at the apex of the heart transmitted to the axilla and injection of the pharynx and tonsillar area, with a few patches of white exudate on each tonsil. No medication was given during the next few days. Chills and fever occurred daily. The patient complained of generalized aches and pains. There was no evidence of any joint involvement. On December 4 the administration of sulfathiazole (1 Gm. four times a day) was instituted, with little effect on the patient's

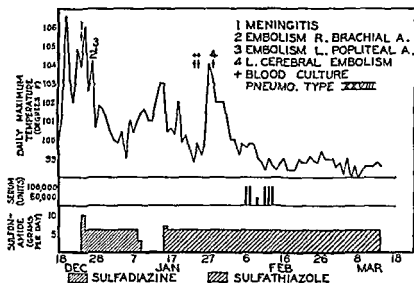


Fig. 1.—Patient's course in the hospital.

(Blumberg, N., et al. J A M A)

clinical signs or symptoms. On December 10, sulfadiazine (1 Gm. four times a day) was begun. On December 13 the patient complained of pain in the calf of the right leg. Examination at that time revealed only tenderness of the right calf. There was no discoloration, swelling, or limitation of motion, and no alteration of pulses in the extremity. The injection of the throat gradually subsided, the exudate disappearing. The murmur previously described persisted. Because of the persistence of the chills, fever, and sweats, the intensity of the murmur and the possible

embolism to his right leg, the patient was hospitalized with a tentative diagnosis of bacterial endocarditis.

Examination: The patient was thin and on admission to the hospital did not appear in acute distress. His temperature was 99.8° F., the pulse rate 100 a minute, and the respiratory rate 20 a minute. There was no dyspnea, cyanosis, jaundice, or lymphadenopathy. No petechias were visible. There was a scar on the left cornea extending from 10 o'clock on the limbus to the center, with anterior synechias. The fundi were normal.

The tonsils were not enlarged and the pharynx was slightly injected. The oral hygiene was poor. Several teeth were missing and several others contained cavities. On the gum above the left lateral upper invisor was a small white spot which was slightly tender but from which nothing could be expressed. The chest was clear. The heart was not enlarged and no thrill was felt. The rhythm was regular, the sounds being of good quality. A loud, rasping systolic murmur was heard at the apex and was transmitted toward the axilla. The second sound at the pulmonic area was accentuated and split. The blood pressure was 110 mm. of mercury systolic and 70 mm. of mercury diastolic.

The liver and spleen were not palpable. There was no tenderness of the costovertebral angle. Rectal examination was negative. There was no edema of the extremities. Pulsations in the dorsalis pedis and posterior tibial arteries were good and equal on the two sides. There was slight tenderness in the calf of the right leg. Neurologic examination was negative.

Course: The course in the hospital is shown graphically in the chart. The day after admission the patient felt fairly well, his temperature reaching only 101.4° F. Laboratory studies revealed a normal urine, blood sugar, blood urea nitrogen, and a negative Wassermann reaction of the blood. The blood count was hemoglobin (Sahli) 12.8 Gm. per 100 cc. (93 per cent), erythrocytes 4,600,000 per cm., and leukocytes 18,500 per cm., with a differential count of 87 per cent neutrophils and 13 per cent lymphocytes. The blood sulfadiazine level was 2.72 mg. per 100 cc. The blood sedimentation rate (Cutler) was 26 mm.

in one hour. An electrocardiogram was normal. By roentgen examination the heart shadow and lung fields were normal.

On December 20 and once or twice daily thereafter, for about ten days, the patient experienced severe shaking chills, following which his temperature would rise to a peak of 102° to 106° F. He would then perspire profusely, with a concomitant fall in temperature. Blood cultures taken before and during the chills showed no growth.

On December 24 the patient complained of headache and a stiff neck. Nuchal rigidity was present and a positive Kernig sign was elicited. Examination of the ears, nose, and throat was negative. No focal neurologic signs were present. Otherwise the examination was as noted on admission. Lumbar puncture revealed a cloudy spinal fluid under a pressure of 190 mm. of water. The fluid contained 18,000 leukocytes per cm., with a differential count of 95 per cent polymorphonuclears and 5 per cent lymphocytes. The chlorides were 700 mg. per 100 cc.; Fehling's solution was not reduced, and the protein was 250 mg per 100 cc. No organisms were seen on smear and there was no growth on culture. Sulfadiazine was then given by mouth. 10 Gm. on December 24 and then 1 Gm. every four hours day and night. The symptoms and signs of the meningitis cleared rapidly during the next few days, but the chills and fever persisted. The blood sulfadiazine concentration was maintained at about 10 mg. per 100 cc. On December 26 the spinal fluid contained 900 cells per cm., with 80 per cent polymorphonuclears and 20 per cent lymphocytes. The chlorides were 650 mg., the sugar was 85 mg., and the proteins were 50 mg. per 100 cc. The sulfadiazine level in the spinal fluid was 5 mg. A smear showed no organisms and cultures were again sterile.

On December 27 the patient complained of sudden pain in the upper inner portion of the right arm and of numbness and coldness of the right forearm and hand. On examination, the right forearm and hand were cold and mottled blue. There was tenderness in the upper inner portion of the right arm. No

pulsation was felt in either the right radial or the brachial artery. A faint pulsation was felt in the right axillary artery.

With the oscillometer, very slight oscillations of the needle were noted in the right upper extremity, with normal oscillations on the left. Papaverine hydrochloride was administered in doses of 0.032 Gm. ($\frac{1}{2}$ grain), at first intravenously and then orally. Also, the affected extremity was wrapped in lamb's wool and placed in a heat cradle. Following the institution of these measures, the pain diminished and the color and temperature improved.

The following morning, December 28, the patient complained of sudden pain in the calf of the left leg. The left foot was cold and blanched and there was tenderness in the upper portion of the calf. No pulsation could be felt in the left posterior tibial, dorsalis pedis, or popliteal artery, but there was good pulsation in the femoral artery. Oscillometric readings were zero below the knee, normal above. A paravertebral block with procaine hydrochloride at the level of the first, second, and third lumbar vertebrae on the left was instituted, papaverine hydrochloride continued, and heat applied.

On January 1, 1942, reappearance of pulsations was noted in the right brachial and radial arteries and the left posterior tibial artery. The pulsations gradually increased in strength, but the difference from those in the unaffected extremity could easily be detected.

The patient's temperature continued to range between 98° and 101° F. Subjectively he felt well. The heart remained normal in size and the murmur changed slightly with variations in the heart rate, but otherwise it was constant. No petechias were noted. The spleen was not palpable. The leukocyte count remained about 10,000 per cmm. The erythrocytes gradually fell to 3,100,000 per cmm. Blood cultures, both aerobic and anaerobic, persistently failed to show growth even though observed up to 16 days. Paraaminobenzoic acid was added to the media when the patient was receiving the sulfonamides. On January 5 the spinal fluid was clear under normal pressure and contained no

cells. The sulfadiazine concentration on that day was 4.6 mg. in the spinal fluid and 7 mg. in the blood. On January 5 and 7 the urine contained many red blood cells and on the latter date many crystals of sulfadiazine also. On January 8 the sulfadiazine was stopped, a total of 97 Gm. having been administered in the hospital.

The patient's temperature then gradually rose and on January 14 reached 103° F. The next day sulfathiazole was started with a dose of 2 Gm. and then 1 Gm. every four hours. His condition remained essentially unchanged, except for some lessening of his fever, until January 28, when a right hemiplegia suddenly developed, involving the face and upper and lower extremities. There was a pronounced motor aphasia, but consciousness was not lost. The next day, January 29, the blood culture taken on January 23 was reported as showing a growth of pneumococcus type XXVIII. The blood culture taken on January 24 was subsequently reported to show a growth of the same organism. Twenty cc. of blood were taken for each of these cultures ten minutes after the subcutaneous administration of 3 minims (0.2 cc.) of epinephrine. On smear of the colonies the organisms were gram-positive encapsulated diplococci. The cultures were bile soluble and on inulin produced both acid and a coagulum. Mice were readily killed after intraperitoneal injection of the cultures. The organisms in the peritoneal washings gave a prompt quellung reaction with type XXVIII pneumococcus serum.

On February 3 the peak of the patient's temperature was below 100° F., and after February 8 never rose above 99.4°. Sulfathiazole, 1 Gm. every four hours, was continued. Between February 6 and 13, 540,000 units of type XXVIII antipneumococcus rabbit serum was administered intravenously (100,000 units each on February 6 and 7, 40,000 units on February 9 and 100,000 units each on February 11, 12, and 13). Intradermal and ophthalmic sensitivity tests were negative and the patient had very little reaction except for a moderately severe chill after the first dose. After February 6 the leukocyte count

remained under 10,000 per cmm. The erythrocyte count gradually rose. The sedimentation rate, however, continued persistently rapid. The patient's murmur remained constant. He was alert, although the aphasia persisted to a strong degree. Heat and massage were administered to the paralyzed limbs. He regained fair motion of the right lower extremity, but very little of the right upper extremity. Spasticity, hyperactive reflexes, and pathologic reflexes persisted in both.

On March 13 his leukocyte count was 7000 per cmm. and his erythrocyte count 4,300,000. Urinalyses were repeatedly negative. The blood sulfathiazole level had been maintained between 4 and 6 mg. per 100 cc. Twenty blood cultures taken subsequent to the positive ones were all sterile.

On March 14, three months after admission, the patient was discharged from the hospital with a diagnosis of type XXVIII pneumococcus endocarditis, with emboli to the meninges, right brachial artery, left popliteal artery, and left middle cerebral artery.

Subsequent Course: Since discharge the patient has shown gradual but steady improvement. Sulfathiazole was continued in gradually decreasing doses and was stopped on April 21. He is able to walk, but the leg is still somewhat spastic. There has been a slight improvement in the right arm. The aphasia is gradually diminishing. The murmur is still easily audible, but appears not quite so rough or loud. There have been no further embolic phenomena. Pulsations in the vessels of the right arm and left leg are still noticeably diminished. His temperature, pulse rate, blood count, urinalysis, and sedimentation rate are all normal. Several more blood cultures taken since his discharge have been sterile. The patient feels well and at present is attending a special school where reëducation is being attempted.

Comment: We feel that a diagnosis of type XXVIII pneumococcus endocarditis is justifiable on the following grounds: (1) The absence of a history of previous heart disease and the normal cardiac findings in another hospital a year prior to the onset

of his present illness; (2) the septic course; (3) the type of murmur; (4) the embolic phenomena, and (5) the recovery of type XXVIII pneumococci in two separate blood cultures.

The origin of the pneumococci is obscure; that the patient did not have pneumonia is definite. Other possibilities are the fistula over the left lateral upper incisor and the infected tonsils and pharynx.

We believe that recovery has occurred on the basis of: (1) The return to normal of the temperature, leukocyte, and erythrocyte counts; (2) the absence of further embolic phenomena; (3) the persistently negative blood cultures, and (4) the pronounced improvement in the patient's general condition.

The relationship to recovery of the therapeutic agents employed is open to question. During the administration of sulfadiazine there was diminution in the chills and fever, which, however, recurred when the drug was discontinued. The embolic phenomena and the positive blood cultures were obtained during active treatment with sulfathiazole. Concomitant with the administration of type-specific rabbit antipneumococcus serum, in addition to the sulfathiazole, the temperature declined and recovery ensued. Whether the serum was instrumental in bringing about recovery or whether the administration was coincidental to spontaneous recovery is a moot point.

REFERENCE

1. BLUMBERG, N.; HEINE, W. I., AND LIPSHUTZ, J.: J. A. M. A. 120:607 (Oct. 24) 1942.



ENDOPHTHALMITIS

See page 265



EPIDEMIC KERATOCONJUNCTIVITIS

See page 267

ERYSIPELAS

Shank, Maxwell, and Bozalis¹ report on the treatment of 165 cases of erysipelas with sulfonamides.

Sulfanilamide was the chemotherapeutic agent used in 102 cases, sulfamethylthiazole in 29 cases, and a new acyl derivative of sulfanilamide, S-22, or sulfabenamide, was given in 34 instances. The dosage of these drugs was as follows:

Two-tenths Gm. per kg. of body weight up to a maximum of 8 Gm., divided into six equal doses and given every four hours for the first 24 hours.

Fifteen one-hundredths Gm. per kg. of body weight to a maximum of 6 Gm. in the second 24 hours.

One-tenth Gm. per kg. of body weight to a maximum of 4 Gm. daily for the duration of the hospital stay.

In addition to chemotherapy, cold boric acid packs were used routinely to relieve pain and discomfort. To prevent recurrence of the lesion, patients were hospitalized from seven to ten days and kept on drug therapy the entire time.

The age and sex distribution, with mortality figures for each group, are presented in Table 1. It will be noted that the majority of these patients were over 40 years of age. It is well understood that erysipelas is especially fatal to the aged and to very young infants. In this series there were only four patients under 2½ years of age. Two of these infants, however, nine months and three months of age, had extensive erysipelas that responded promptly to drug therapy.

There were five deaths in the group of 165, a mortality figure of three per cent. This compares with mortality rates of from 8 to 12 per cent before the use of sulfanilamide as reported by others. Necropsies were done in four of the fatalities. In each instance there were complicating disease processes. These are listed in Table 2.

Blood concentrations of the drug used for these patients varied between 8 and 16 mg. per 100 cc. In each instance the local lesion was seen to regress with the treatment outlined. In case 3 the blood culture showed growth of the hemolytic streptococcus

TABLE I—AGE AND SEX DISTRIBUTION WITH MORTALITY FIGURES

<i>Age</i>	<i>Number</i>	<i>Sex</i>	<i>Deaths</i>
Birth to 2½ years	4	Male. . . . 4 Female 0	0 0
2½ years to 15 years	10	Male 5 Female 5	0 0
15 years to 40 years	25	Male 9 Female 16	0 0
40 years to 60 years	64	Male 34 Female 30	1 0
60 years to 70 years	44	Male 25 Female 19	4 0
70 years and over	18	Male 11 Female 7	0 0
Total	165		

(Shank, R. E., *et al* J. A. M. A.)

on entry, but subsequent cultures produced no growth. Vegetations of bacterial endocarditis were found present in case 4. Blood cultures had been negative. In case 5 death was sudden and due to hemorrhage from a free-bleeding acute duodenal ulcer demonstrated postmortem. All other deaths were due to the complications of degenerative disease that had not responded to the usual modes of therapy. Four of the deaths occurred in the group of 102 patients who were treated with sulfanilamide, a mortality rate of 3.9 per cent. One death among 29 patients getting sulfamethylthiazole gave a 3.4 per cent mortality for this drug, while no fatalities have developed in the sulfabenamide-treated series of 34 patients.

Of the 160 patients treated successfully, spread of the lesion was never noted after the first 36 hours of treatment. In general the erythema and induration were definitely subsiding after 48 hours, although some brawniness was present for from five to seven days.

In 84 cases with initial fever the temperature was normal within 24 hours after beginning drug therapy and remained so throughout hospitalization. Fever persisted for 48 hours in 49

TABLE 2—CASE SUMMARIES OF THE FIVE FATALITIES

<i>Case No. & Age</i>	<i>Color; Sex</i>	<i>Complicating Diseases</i>	<i>Drug Used</i>	<i>Autopsy</i>
1 62	White ♂	Chronic nephritis, bronchopneumonia	Sulfanilamide	Yes
2 63	White ♂	Aortic aneurysm, degenerative heart disease, cardiac decompensation	Sulfanilamide	Yes
3 54	White ♂	Degenerative heart disease, auricular fibrillation, cardiac decompensation	Sulfamethyl-thiazole	No
4 63	White ♂	Degenerative heart disease, cardiac decompensation, bacterial endocarditis, acute glomerulonephritis, thrombosis of right pulmonary artery	Sulfanilamide	Yes
5 62	White ♂	Acute duodenal ulcer, massive gastrointestinal hemorrhage, degenerative heart disease	Sulfanilamide	Yes

(Shank, R. E., et al. • J. A. M. A.)

patients, for 72 hours in 12, and in four patients for as long as four days. Thus fever persisted longer than 48 hours after treatment was begun in only 16 cases, or in 9.7 per cent of cases treated.

Only one complication was seen in the entire series, a small subcutaneous abscess beneath the eye, requiring incision and drainage. This abscess developed at the site of the erysipelas, in the region of an infected squamous-cell carcinoma. There were no recurrences of erysipelas lesions.

Rantz and Keefer, in their report, stated that complications occurred most frequently in those patients who did not receive the drug until late in the course of the illness. This has not been our experience. Treatment was begun with the history of the lesion existing from 12 hours to 14 days before admission in our group of patients. Response of the individual lesion to sulfanilamide was universally prompt regardless of its duration.

As already noted, sulfanilamide was given to 102 of the 165 patients reported in this series. This drug is inexpensive, but has the disadvantage of producing toxic symptoms, particularly

in older persons. Nausea and methemoglobinemia were frequent. There were occasional occurrences of toxic psychoses with complete disorientation of the patient. Infrequent cutaneous rashes were seen.

Sulfamethylthiazole, although never put on the market and now prohibited from further clinical use, gave excellent results in 29 cases. It was found, in general, to be somewhat less toxic than sulfanilamide. No peripheral neuritis was seen in this small group of patients.

TABLE 3—DURATION OF FEVER AFTER THERAPY WAS BEGUN

<i>Number of Patients</i>	<i>Febrile Period After Beginning Chemotherapy</i>	<i>Percentage</i>
84	24 hours	50.9
49	48 hours	29.7
12	72 hours	7.2
4	96 hours	2.4
16	Afebrile throughout	9.7
165		

(Shank, R. E., *et al.*: *J. A. M. A.*)

We have no evidence that sulfabenamide has wide applicability as a therapeutic agent. In erysipelas, however, it seems to be as valuable as sulfanilamide or sulfamethylthiazole, and in our limited experience it was gratifyingly free from toxic effects. None of the 34 patients had any apparent methemoglobinemia, and there were no gastrointestinal disturbances. Two morbilliform cutaneous rashes were seen, but disappeared despite continuance of the drug. Mental confusion, so frequently seen in aged persons when given sulfanilamide, was not observed with this new drug.

See also page 132.

REFERENCE

1. SHANK, R. E.; MAXWELL, R. W., AND BOZALIS, G. S.: *J. A. M. A.* 117: 2238 (Dec. 27) 1941.

ERYTHEMA MULTIFORME

See page 171



FILARIASIS

Earle¹ cites three cases of lymphadenitis complicating filariasis successfully treated with sulfapyridine. The striking beneficial effect of sulfapyridine on the lymphadenitis probably indicates that the complication is due to a secondary streptococcic infection rather than to the filariasis itself. This is borne out by the fact that the number of microfilarias in the blood stream was not reduced by the drug.

REFERENCE

1. EARLE, K. V.: *J. Trop Med.* 2:667 (Nov. 29) 1941.



FRACTURES

The results with compound fractures, says Matuska,¹ have been much more satisfactory since sulfanilamide has been used locally in the wounds after they have been thoroughly cleansed and débrided. These patients have all been given sulfanilamide or sulfathiazole by mouth also, complementary to the use of sulfanilamide locally in the wound. Open reductions of fractures have done much better also, and there has not been a single case of infection in an elective open reduction since sulfanilamide has been placed in the operative wound. The sulfonamides probably act largely as a bacteriostatic agent, and they help to tide the patient over the critical period during which his defenses are lowered. That is why they are of such value to the wounded soldier, since they keep down infection during the period after the injury, while a patient is being carried from the battlefield and transported to the first-aid station. Then, when the physiology of the body is again approaching normal, the patient is in better condition to win his own personal battle against infection. The early use of sulfanilamide is made pos-

sible for the soldier by the fact that sulfanilamide powder and tablets are included in his own individual equipment which he carries with him.

In the Year Book for General Surgery for 1939 there is reported a series of 39 compound fractures in which sulfanilamide was implanted locally in which there was not a single infection, while in another series of open fractures treated without sulfanilamide 27 per cent showed infection, seven cases had gas, and five needed amputation.

REFERENCE

1. MATUSKA, WALTER H.: Kentucky M. J. 41:231 (July) 1913.



FURUNCULOSIS

In the treatment of furunculosis with sulfonamides one should carefully evaluate the severity of the infection with the possibility of toxic reactions from the drug. As a general proposition, it probably is not wise to treat a single boil or even several with sulfonamide therapy. Likewise, sulfonamide therapy is apt to prove disappointing. If treatment can be given early in these cases, x-ray therapy is more desirable.

In extensive furunculosis, sulfathiazole is the drug of choice. The initial dose is 3 to 4 Gm. orally, followed by 1 Gm. every six hours day and night. The full effect of the drug will be achieved within four to five days, when it should be discontinued.



GAS GANGRENE

Reed and Orr¹ have demonstrated the marked therapeutic effects of sulfonamides, particularly sulfathiazole, used locally in guinea pigs experimentally inoculated with ten times the lethal dose of *Clostridium welchi*, *Clostridium septicum*, *Clostridium novyi*, or *Clostridium sordelli*. The drug was placed in the depth of the wound. Concentration of sulfathiazole remained high in the wound for a longer period than was the case

with the other sulfonamides. The relatively stable concentration of sulfathiazole in the infected or potentially infected tissue probably was an important factor in the superiority of sulfathiazole over the other sulfonamides. Sulfathiazole used orally resulted in 60 per cent recoveries and when introduced directly into the infected wounds it brought about 97 per cent recoveries. The untreated animals died within 26 hours of characteristic gas gangrene.

The report of McIntosh and Selbie,² on the other hand, is not so favorable. They state that prophylactic and therapeutic chemotherapy has failed to show an appreciable reduction in the incidence of gas gangrene. Most of the experimental anaerobic infections used as tests, they say, are not severe enough to be comparable with the disease in man. They tried to overcome this by devising a standard severe infection in mice, producing the disease by the intramuscular injection of 100 minimal doses of the bacteria with calcium chloride as a stimulant, followed an hour later in the same site by an injection of the chemotherapeutic drug under test. The one-hour interval gives consistent results with repeated tests.

The chemotherapeutic agents giving the most effective results against the individual infections were penicillin against *Clostridium perfringens* and *Clostridium oedematiens*, and sulfathiazole against *Clostridium septicum*. No drug tested was equally effective against all three of the organisms. The best prophylaxis was accomplished by a mixture of drugs, and experience suggests the local application of a mixture of sulfathiazole and proflavine. Owing to the rapidity with which gas gangrene spreads, the value of local therapy becomes restricted, and general treatment, including antitoxins, is essential.

REFERENCES

1. REED, G. B., AND ORR, J. H.: War Med. 2:59 (Jan.) 1942.
2. MCINTOSH, J., AND SELBIE, F. R.: Lancet (London) 1:793 (June 26) 1943.

GONORRHEA

In no other division of therapeutics has chemotherapy with the sulfonamides so almost completely supplanted all the older forms of treatment. With the advent of sulfanilamide it was thought that at last the ideal drug had been found for gonococcal urethritis. Discharge cleared promptly and most patients were apparently cured within a few days.

Experience proved, however, that sulfanilamide had not answered all problems of gonorrheal therapy. Many cases merely had their symptoms masked while their infection remained. Others promptly relapsed. All in all, sulfanilamide in gonorrhea soon showed that it was going to be a menace rather than a benefit, for too many patients were released from treatment with seeming cures only to spread their infection far and wide.

The use of sulfapyridine was an improvement in gonococcal therapy. The cure rate of ambulant patients became much higher and there were fewer relapses. However, the greater toxicity of the drug puts some limitation on its use.

Today sulfathiazole is the sulfonamide of choice in gonorrhea, although the *sine quo non* probably has not been reached. Newer sulfonamides are in the offing which may take its place. It is conceded that if sulfathiazole is to produce a cure, it will do so within one week of its initial administration in sufficient dosage. It must be remembered that the sulfonamide drugs in some persons will reduce the activity of gonorrhea and prevent its extension, but will fail to banish completely the objective symptoms. A few patients will show no beneficial effects at all from the sulfonamides at the time of administration. This failure to react favorably may be a transient state and a later course of the drug may quickly render the patient symptom-free or even bring about a cure. However, if no effect is observed from the sulfonamides, one should resort to the older methods of treatment.

The total optimum dosage of sulfathiazole in a course of treatment is 20 Gm. (300 grains). The following scheme of treatment is recommended for ambulant patients:

Day of treatment	1	2	3	4	5
Total daily dosage in Grams. . . .	4	4	4	4	4

Most toxic symptoms occur after the first week of treatment, so that it is inadvisable to continue therapy after the five days indicated above. If objective symptoms are not entirely absent at this time, the case should be regarded as a drug failure. After a week's rest sulfathiazole may be tried again for five days under the same scheme. The daily dose of 4 Gm. is usually divided into four equal parts and given orally, 1 Gm. (15 grains) after each meal and at bedtime. The five-day course is started as soon as the diagnosis of gonorrhea has been made.

It will be noted that nothing has been said of blood concentration of sulfathiazole. This does not have the importance that it has in the treatment of pneumonia and some other diseases. Failures have been observed in patients with a high blood concentration of the drug and gratifying cures in others whose blood concentration never went beyond 1.5 mg. per 100 cc. of blood.

Untoward Reactions: Despite the lower toxicity rate of sulfathiazole, it should be borne in mind constantly that there are patients who cannot tolerate it or any other sulfonamide. For this reason, patients not only should be warned of the possibility of toxic reactions, but should be seen by the physician every 48 hours while taking the medicine. Should fever, rash, or vomiting occur, the drug should be withdrawn immediately and the fluid intake greatly increased. The following mild reactions may occasionally be noted which do not necessitate the withdrawal of the drug: Nausea, headache, vertigo, weakness, malaise, nervousness, and insomnia. Blood studies need be performed only when there is evidence of a severe reaction.

The danger of renal tubular deposits of sulfathiazole crystals is nearly nonexistent with the above scheme of treatment, and particularly if the daily fluid intake is in excess of 1000 cc. Few ambulant patients take less than this amount of fluid per day, but it might be wise to question them when treatment is started and make sure that they ingest a sufficient quantity of fluid.

TABLE 1.—VENEREAL DISEASE RATES IN CONTROL AND SULFATHIAZOLE TEST GROUP AT FORT BENNING
(All rates per thousand per annum)

Month	Number in Group	Gonorrhea		Chancroid		Syphilis		Total	
		Cases	Rate	Cases	Rate	Cases	Rate	Cases	Rate
1. Control Group (No Sulfathiazole)									
March	3771	68	216	38	121	15	48	121	385
April	1883	51	325	19	121	13	83	83	529
May	3975	48	145	22	66	17	51	87	262
June	4101	60	176	15	44	13	38	88	258
July	4395	80	218	30	82	39	106	149	406
August	5100	63	148	10	24	25	59	98	231
September	5069	43	102	13	31	16	38	72	170

2 Test Group, Including All "Failures"									
March	1200	18	180	6	60	5	50	29	290
April	1560	28	216	15	115	4	31	47	362
May	1565	5	38	7	54	3	23	15	115
June	1555	5	38	2	15	8	62	15	115
July	1440	4	33	6	50	7	58	17	141
August	1200	7	70	3	30	1	10	11	110
September	1223	1	10	4	39	4	39	9	88

3. Test Group, Omitting "Failures" Not Under the Sulfathiazole Medication as Prescribed									
March	1200	18	180	7	60	5	50	29	290
April	1560	28	216	15	115	4	31	47	362
May	1565	1	8	1	8	3	23	5	39
June	1555	1	8	0	0	8	62	9	70
July	1440	1	8	1	8	7	58	9	74
August	1200	1	10	1	10	1	10	3	30
September	1223	0	0	0	0	4	39	4	39

(Loveless, J. A., and Denton, Wm. J. A. M. A.)

This necessity to watch the fluid intake and the urinary output carefully becomes very important in tropical and subtropical places and during hot weather anywhere. Profuse perspiration markedly diminishes the amount of urine passed by the kidneys and greatly increases the possibility of a blockage of the urinary

passages by deposits of sulfathiazole crystals. In order to guard against this one should make sure that the patient under sulfathiazole therapy passes a minimum of 1000 cc. of urine in 24 hours.

Oral Sulfathiazole Prophylaxis: Joses¹ reports on the use of sulfathiazole in divided doses as a prophylaxis against gonorrhea after exposure. The drug was given to 350 men, none of whom developed the disease.

The series of Kline and Ryan² was larger, 1000 men. Of these, three developed gonorrhea.

A more recent study was made by Loveless and Denton³ on 1400 Negro soldiers, using 4000 Negro troops from the same post as a control.

The method of administering sulfathiazole was as follows: All soldiers in the test group were required to "sign out" and "sign in" through the noncommissioned officer in charge of quarters. On signing out, each soldier was given 2 Gm. (30 grains) of sulfathiazole and was observed to swallow it in the presence of the noncommissioned officer. During the first few weeks of the study all soldiers who did not have in their possession a copy of form 77 MD (station prophylaxis slip) on signing in were given a dose of 2 Gm. (30 grains) of sulfathiazole and an additional 2 Gm. (30 grains) the following morning under the same strict supervision. Later this exemption on the basis of station prophylaxis was discontinued and sulfathiazole was administered to all. Early in the course of the experiment restriction to camp for a period of one week of those who received 6 Gm. (90 grains) was attempted in order to prevent overdosage. This restriction was later relaxed. The cost of this prophylaxis has been about ten cents per soldier monthly.

Table I presents the rates for gonorrhea, chancroid, and syphilis of the test and control group from March through September. The administration of sulfathiazole to the test group was started on May 1.

It will be noted that in the control group there is no distinct trend of the rates for gonorrhea or syphilis. The rate for chan-

croid is considerably lower during the last four months of the total period.

Section 2 of the table includes all cases of venereal disease diagnosed during the period March through September. The decline in the gonorrhea rate is evident. Chancroid shows no clear-cut change, and syphilis remains constant, except during the month of August, when a sharp decline is noted. Section 3 excludes those cases not under the influence of sulfathiazole when exposure occurred—men who were exposed away from the post while on overnight leave or furlough and who could therefore not obtain the additional sulfathiazole that would have been given could they have returned to the post. These cases are counted in section 2, as they were members of the group under study, but are omitted from section 3 because of their failure to carry out the provisions of the study. One gonorrhea failure was noted in each of the months of May, June, July, and August. The situation is similar with chancroid infection. When sulfathiazole was taken according to the plan of the experiment, gonorrhea and chancroid almost entirely disappeared. Syphilis was unaffected, although the low rate noted in August is not explained.

Sulfonamide-resistant Gonorrhea: Herrell, Cook, and Thompson⁴ report on the use of penicillin in sulfonamide-resistant gonorrheal infections. We have studied experimentally, they say, the antibacterial activity of penicillin against several strains of *Neisseria gonorrhoeae* isolated from patients in whom the infection was completely resistant to what might be considered adequate treatment with sulfonamide preparations. These strains of organisms are inhibited completely in fairly high dilutions of an active form of penicillin. Bacterial cultures reveal that the number of organisms is decreased greatly at the end of one or two hours' contact with penicillin. Between the second and third or third and fourth hours in contact with penicillin no viable organisms were found. This experimental evidence immediately suggests that penicillin should prove

effective in the treatment of clinical infections due to these sulfonamide-resistant bacteria.

The complete absence of toxicity following the intravenous administration of pyrogen-free penicillin, the lack of any discomfort to the patient and the rather rapid disappearance of clinical symptoms have been observed in three cases of sulfonamide-resistant gonorrheal infections. Because of the limited amounts of penicillin available, we feel that penicillin therapy should be reserved and studied further in those cases in which the infection is resistant to the accepted forms of treatment now being used. In all the cases reported, in addition to the clinical response noted, negative bacterial cultures were obtained sometime between 17 and 48 hours after the institution of penicillin therapy.

Gonorrhea in the Female: Fletcher, Gibson, and Sulkin⁵ report on the treatment of 194 women with gonorrhea. Four Gm. of sulfathiazole were given in divided doses of 1 Gm. each four times a day for five consecutive days. Medication was begun as soon as the diagnosis of gonorrhea was established, without regard for the phase of the menstrual cycle. A second course of treatment was given as a routine during the following period of menstruation. If menstruation occurred during the first administration of the drug, medication was not repeated during the subsequent period. When it did not occur before the patient was discharged from the hospital, she was given enough sulfathiazole for another course of therapy to be taken during her next menstrual period. This precaution was taken because preliminary observations suggested that menstruation may be responsible for an exacerbation of the infection.

Every case was classified as chronic gonorrhea with the exception of two in which there was an acute inflammation of the cervix, urethra, and both adnexae associated with a severe febrile reaction. The cases classified as chronic gonorrhea presented no symptoms. This is in contradistinction to those classifications wherein the mere finding of a positive slide or culture warrants a diagnosis of acute gonorrhea.

Forty-five per cent of the patients had a gonorrheal infection of the cervix alone. In 12 per cent only the urethra was involved, while 43 per cent had both cervical and urethral infections. Every patient in whom the pelvic adnexae were present showed some type of chronic inflammatory condition.

Ninety-one and two-tenths per cent of the total number of patients under observation at the end of the "quarantine parole" period (12 weeks) were considered clinical cures.

Local Use of Sulfathiazole: Stedman⁶ used microcrystalline preparations of sulfathiazole in the local treatment of gonorrhea in women because of the ease of application, the property of remaining in a milklike suspension, and the absence of a tendency to clump and cake. The method of treatment was as follows:

(1) Treatments were given once daily. The mucopurulent exudate was removed from the cervix and vagina with a dry sponge. (2) Three methods of application of microcrystalline sulfathiazole were used: (a) By means of a powder blower the cervix and vagina were coated with microcrystalline sulfathiazole; (b) 2 or 3 cc. of a five per cent solution of microcrystalline sulfathiazole were instilled into the vagina; or (c) a suppository of ten per cent microcrystalline sulfathiazole was inserted into the vagina. This suppository takes about ten minutes to dissolve, spreads out over the entire cervix and vagina, and remains for several hours. The glycerin suppository was found to be the best form of application. (3) About 5 cc. of a five per cent suspension of microcrystalline sulfathiazole were instilled into the urethra. This plan of treatment resulted in negative smears in from 8 to 31 days. The treatment caused the patients no inconvenience except the daily attendance at the clinic. No evidence of irritation or inflammatory reaction from the drug resulted.

The author also used a five per cent suspension of microcrystalline sulfathiazole instilled into the urethra as a prophylaxis against gonorrhea in the male and found it effective in 99 per cent of 297 males. He suggests the use of vaginal suppositories of microcrystalline sulfathiazole as a prophylaxis against gonorrhea in order to protect both parties of the sexual union.

Present Status of Gonorrheal Therapy: While the outlook for the patient with gonorrhea is far better than it was a few years ago, the ideal therapeutics has not yet arrived. Sulfathiazole will give a cure rate in carefully controlled cases of well above 80 per cent, which is far better than could be achieved under older forms of treatment, but there still remains that small percentage of cases which are not benefited. In addition, there is a definite percentage of cases who become symptomless carriers of gonorrhea following sulfathiazole therapy. Symptomless carriers, whether they be male or female, are a menace against whom there is little protection and who form a nidus for a constant dissemination of infection.

Some hope has been aroused through recent medical and magazine articles that penicillin will be the answer to the gonorrhea problem once this drug is available for civilian use. However, even after large pharmaceutical houses can concentrate on its manufacture, it will continue to be far too expensive for general use. The very cost of this comparatively new remedy will compel the overwhelming majority of sufferers from gonorrhea to continue to rely upon sulfathiazole, with its dangers of toxic manifestations and its rather small number of failures. Likewise, the technic of penicillin therapy in gonorrhea is not a simple matter and will not be adaptable for use in most cases of the disease. Finally, from the meager reports available, it is evident that penicillin is not a 100 per cent effective agent against gonorrhea.

Possibly with the present intense interest in chemotherapy, some new sulfa drug or some totally different therapeutic agent will be introduced which will entirely solve the problem of gonorrhea. Possibly, too, with the availability of penicillin after the war, it can be used to clear up the small percentage of cases in carefully controlled series which do not respond completely to sulfathiazole therapy. (It must be remembered that the figures are not so optimistic in ambulant cases.) Nevertheless, whatever the future may hold for the conquest of gonorrhea, it still is a problem that demands far more from the phy-

sician than the haphazard distribution to his patients of a handful of tablets. Like all great advances in Medicine, sulfonamide therapy has opened new problems to keep us on our toes to find a solution.

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3. LOVELESS, J. A., AND DENTON, WM.: J. A. M. A. 121:827 (March 13) 1943.
4. HERRELL, W. E.; COOK, L. N., AND THOMPSON, L.: *Ibid.* 122:289 (May 29) 1943.
5. FLETCHER, P. F.; GIBSON, O. J., AND SULKIN, S. E.: *Ibid.* 117:1769 (Nov. 22) 1941.
6. STEDMAN, H. E.: U. S. Nav. M. Bull. 41:1118 (July) 1943.



HEAD INJURIES IN WAR

Generous use of sulfanilamide, says Cloward,¹ not only in the scalp and skull wounds, but also in the missile tract in the brain, is recommended. Sulfanilamide is preferred to other sulfonamides because it has been found to be much more rapidly absorbed into the blood stream from an open wound than any of the other sulfonamide drugs.

The dosage of sulfanilamide applied locally is 1 Gm. for each ten square inches of surface involved, but in closed cavities not more than 5 Gm. should be used. At no time should more than 15 Gm. be used locally, for the drug is absorbed rapidly and toxic reactions can readily develop.

REFERENCE

1. CLOWARD, R. B.: J. A. M. A. 118:267 (Jan. 24) 1942.



HIDRADENITIS SUPPURATIVA

See page 170



IMPETIGO CONTAGIOSA

See page 173

INFLUENZA

While the sulfonamides have been used frequently in influenza, there is no evidence that they exert a favorable influence on the course of the disease. Also, since the patient receiving the sulfonamides is exposed to their toxic reactions without hope of beneficial result, it would seem better not to administer them in influenzal infections. See *Respiratory Infections*, page 309.



KERATOCONJUNCTIVITIS, EPIDEMIC

See page 267



KERATODERMA BLENNORRHAGICUM

See page 171



LEUKOPENIA, MALIGNANT

Although leukopenia is one of the dangers of sulfonamide therapy, Heilig and Visveswar¹ report the successful treatment of two cases with sulfapyridine. Their comment follows:

It is a generally accepted clinical rule that the sulfonamides are strictly contraindicated in all cases of leukopenia, especially when a granulocytopenia is present. This rule is based on the fact that members of the sulfonamide group tend toward diminishing the number of leukocytes in general and the granulocytes in particular to such an extent that fatal consequences due to acute agranulocytosis have been reported in numerous instances. This danger is supposed to threaten whenever full doses of one of these compounds are used, so much so that leukocyte and differential counts should be performed at short intervals and the application of these drugs stopped at once when the total amount of white cells or the percentage of neutrophils shows a tendency to decrease.

Furthermore, it is well known not only that sulfanilamide, sulfapyridine, and other sulfonamide compounds interfere with

the leukopoiesis, but also that the red blood cell count occasionally shows such a reduction that blood transfusions might be required. Quite recently Chaudhuri found that therapeutic doses of sulfanilamide and sulfapyridine in monkeys cause "a moderate and progressive anemia" and "a consistent decrease of leukocytes." Nevertheless, the reasoning might be justified that a toxic arrest of the leukopoietic activity of the bone marrow, causing leukopenia and granulocytopenia, could be counteracted and the normal marrow function restored if one succeeded in eliminating the source of toxin production. Thus the question arises whether it is probable that the sulfonamides would exert their bacteriostatic action, which inhibits the further release of toxins more rapidly than their paralyzing influence on the bone marrow. Dameshek and Wolfson found in two cases of acute agranulocytosis that sulfathiazole did no harm and that it might have been of value in combating the secondary sepsis, although no definite proof for the latter opinion could be presented because it was given in addition to transfusions and pentnucleotides. So far as two cases can show, small doses of sulfapyridine are capable of improving the rapidly declining leukopoiesis if the infective organisms responsible for the severe toxemia respond promptly to the drug. In our cases such a response was established—apart from the changes in the blood picture—by the fact that the fever subsided immediately and the general condition, which prior to sulfapyridine medication apparently precluded any hope, improved so speedily and completely without the employment of any other treatment that a spontaneous or chance recovery obviously was out of the question.

The course of events leading to this development, unexpected in several aspects, could be reconstructed and the origin of the toxemia traced in the following way: In the first case a hypertrophied prostate gland which, as the patient later stated, had caused typical complaints for the past one year, caused urinary stagnation with a subsequent infection of the urinary tract. A tendency to a low leukocyte count is not rarely seen in coliform group infections, so that an unusually heavy infection, such as

was proved in this case by the onset with a rigor, the high fever, and the delirious condition, might have turned the initial leukocytosis to leukopenia, which renders the system defenseless against a further invasion and unrestrained multiplication of all kinds of pathogenic microorganisms. The second patient suffered from diarrhea which lasted for one year up to her admission. Though it recurred only on the ninth day of her stay in the hospital and lasted for a few days, easily controlled by Plantago seed diet, it is significant that this short attack of diarrhea the very next day was followed by the heaviest febrile attack, with two rigors, the temperature reaching 104.5° F. twice within one day. The explanation is that during the chronic diarrhea which preceded the patient's hospitalization a chronic infection of the urinary tract, proved microscopically and bacteriologically on admission, was established, owing to the increased permeability of the affected mucous membrane of the colon. The acute diarrheal relapse certainly was due to an increased virulence of the intestinal bacterial flora which invaded the urinary tract in force and, most probably, simultaneously entered the systemic circulation. Proof of the former process is the enormous increase of pus cells (4 plus) in a catheter specimen of the urine; the latter—the development of a septicemia—is almost ascertained by the occurrence of six rigors in eight days of high fever, uninfluenced by intravenous administration of quinine. The close connection between diarrhea and subsequent urinary tract infection was experimentally established by Leishman and is noticed in almost all of our diarrhea cases, especially in women. In contrast to the first case, leukopenia of 2400 to 2500 leukocytes per cubic millimeter with a relative lymphocytosis already present was found on admission. The further development clearly shows that this white blood cell picture was due not to some constitutional peculiarity but only to the urinary tract infection, the leukocyte count subsequent to the successful treatment of the septicemia being constant at about 7000 with a normal differential picture. It is noteworthy that the red blood cell count did not improve simultaneously with the leukocytes but required administration

of crude liver extract. In both of these cases small doses (1.5 to 2.5 Gm.) of sulfapyridine succeeded in cutting short the course of the fever and further administration of 2 Gm. a day, making a total of 6.25 Gm. and 10.25 Gm. respectively, in keeping the patient afebrile. It is highly improbable that such doses should have been sufficient to achieve sterilization of the heavily infected urinary tract, the more so as in case 2 *Escherichia coli* was found in the urine after one month of afebrility, normal bowel function, and general well-being. The explanation of the successful medication obviously is that the drug, exerting its generally recognized bacteriostatic action, stopped further bacterial multiplication and prevented a renewed invasion of the circulation as well as further production of toxin, thus enabling the patient's defense mechanisms to deal with the bacteria which already were present in the system when the treatment was started.

When these cases were presented the discussion hinged on whether the development of leukopenia was not precipitated by the intravenous use of quinine and methenamine with sodium salicylate and caffeine with sodium salicylate (Pyelopurin). For the investigation of this question four patients with particularly severe malarial and four with highly febrile urinary or biliary tract infection, all of them in a very low condition, were selected and treated with full doses of quinine or the proprietary methenamine mixture respectively by the intravenous route.

In each of these cases a total leukocyte count and differential picture have been determined before and 12 to 24 hours after conclusion of a course of either five quinine injections, containing 35 grains (2.3 Gm.) of quinine dihydrochloride, or of five ampules of "pyelopurin intravenous," each of them containing methenamine 2 Gm. (30 grains), sodium salicylate 0.08 Gm. (12 grains), and caffeine with sodium salicylate 0.2 Gm. (3 grains). In two of the cases in which quinine was given, the leukocyte count increased; in the other two it remained unaltered. The proportion of neutrophils showed variations of \pm ten per cent with a maximum of 80 and a minimum of 60 per

cent after treatment. Similarly insignificant were the changes following medication with the methenamine mixture. In addition to our eight control patients, the second of our two leukopenia patients received a course of five intravenous injections of the methenamine preparation when after one month of well-being *Escherichia coli* was found in her urine; on conclusion of this medication (January 25) the leukocyte count was 6800, the differential picture 72 per cent neutrophils, 27 per cent lymphocytes, and one per cent eosinophils. These results make it highly improbable that in our cases leukopenia and granulocytopenia should have been due to doses of quinine or methanamine with sodium salicylate and caffeine with sodium salicylate, which were smaller than those used in the control cases, though it cannot be excluded that in rare instances of hypersensitivity against these compounds and a constitutional weakness of the leukopoietic apparatus such a reaction might develop.

REFERENCE

1. HEILIG, ROBERT, AND VISVESWAR, S K. J. A. M. A. 122:591 (June 26) 1943.



LUDWIG'S ANGINA

Conway¹ reports three cases of Ludwig's angina treated with sulfonamides without surgical intervention. In Case I continuous warm dressings were applied to the neck and continuous steam inhalations were given. Fluids were supplied intravenously. Sulfonamide therapy consisted of five intramuscular injections of 5 cc. each of five per cent azosulfamide in the first 24 hours. In addition sulfathiazole, 8 Gm., was given by rectum on admission and 8 Gm. more were given by the same route in two doses in the next 36 hours. The following day the patient could swallow and could take fluids by mouth. One Gm. of sulfathiazole was then given every four hours. Three days after the beginning of the sulfonamide therapy the patient could take soft diet and at the end of 12 days the medication was discontinued. The other two cases had similar treatment and like results.

Some cases, says this author, "obviously will require immediate operation, either tracheotomy or wide incision or both, and preparations for such operations should always be made and held in readiness whenever a patient is admitted with a condition which may rapidly go on to produce respiratory embarrassment. However, in view of the experiences presented in this report, I do not see the necessity for precipitous surgery."

REFERENCE

1. CONWAY, J. F.: J. A. M. A. 118:953 (March 21) 1912.



LUPUS ERYTHEMATOSUS

See page 168



LYMPHANGITIS

See page 167



LYMPHOGRANULOMA VENEREUM

Lymphogranuloma venereum, known also under such synonyms as fourth venereal disease, sixth venereal disease, lymphopathia venereum, lymphogranuloma inguinale, and strumous bubo, is a disease caused by an unknown filtrable virus and usually is venereal in origin. Although known under various names for the past hundred years, until fairly recently it was considered rather a rarity. This no doubt was due to the fact that prior to the Frei test, which will give a positive diagnosis of lymphogranuloma venereum, most cases of rectal stricture were believed to be syphilitic, or to be due to staphylococcic infection, or to ulcerative colitis, or to tuberculosis. Now the true diagnosis is being made with far greater frequency. That the disease is far from being rare is shown by the fact that the late Collier Martin was able to report a series of something over 300 cases collected in a very few years in his clinic in Philadelphia.

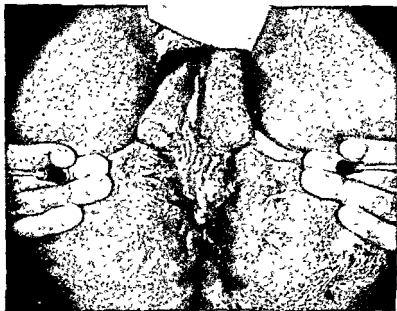


Fig. 1—Lymphogranuloma inguinale. Patient six months pregnant. Positive Frei test. On delivery, the newborn baby also had a positive Frei test.

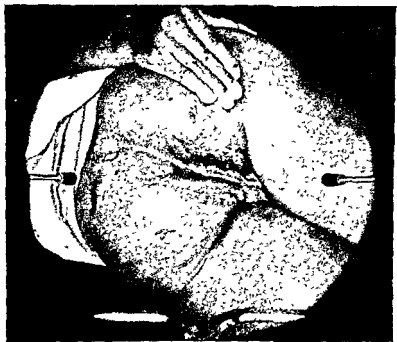


Fig. 2—Same patient as Fig. 1.

it seems more likely that the sulfonamides act on the associated bacterial infection virtually always present, and that the patient relieved of this terrific depression to his entire system is then able by some unknown mechanism, possibly by the building up of an active immunity, to overcome the virus infection.



Fig. 5—Lymphogranuloma inguinale. Same patient as Fig. 4.

A report on the use of sulfanilamide is by Schaffer and Arnold.¹ These authors gave 40 grains daily in four doses of ten grains each for the week; 30 grains daily in three doses of ten grains each for one week; and 20 grains daily in four doses of five grains each for two to six weeks.

TABLE 1.—LYMPHOGRANULOMA VENEREUM INFECTION OF THE RECTUM IN TEN WHITE PATIENTS*

No.	Sex	Age	History of Dobos	Lesion	Tm Reaction, Mm.	Neutral- izing Power of Serum	Isolation of Virus	
							Source of Biopsy Specimen	Result
1.	L. F.	40	Positive	Reddened granular mucosa, stricture 4.5 cm. above anus	10	Strongly positive	Ulcerated mucosa below stricture	Negative
2.	L. P.	40	Positive	Frable, bleeding mucosa; colostomy; rectal stricture	12	Positive	Same, 5 mo. later Lower margin of stricture	Positive Negative
3.	E. P.	38	Positive	No inflammation; smooth stricture 6.5 cm. above anus	13	Very strongly positive	Lower margin of stricture...	Positive
4.	L. C.	33	Positive	Inflamed, bleeding, polypoid mucosa; stenosis of anus	12	Strongly positive	Polypoid area of mucosa..	Positive
5.	G. R.	26	Positive	Stricture 5 cm. above anus; mucosa below chronically inflamed	11	Strongly positive	Lower margin of stricture.. Same, 2½ mo. later.	Negative Positive
6.	M. G.	28	Positive	Granular, bleeding mucosa; mucopurulent exudate; no stricture	7	Strongly positive	Rectal mucosa... Same, 3 mo. later	Negative Negative
7.	F. B.	39	Negative	Numerous superficial ulcerations with bleeding; no stricture	8	Positive	Same, 4 mo. later Rectal mucosa	Negative Negative
8.	B. S.	40	Negative	Granular, bleeding mucosa, no stricture	8	Positive	Rectal mucosa.	Negative
9.	C. C.	41	Negative	Inflamed, friable, edematous bleeding mucosa; profuse purulent exudate; no stricture	7	Positive	Rectal mucosa.	Positive
10.	P. H.	50	Negative	Bleeding mucosa; benign polyps; stricture 4.8 cm. above anus; colostomy	0† 7	Positive Positive	Mucosa below stricture... Same, 13 mo. later.	Negative Unsatisfactory

*The cases of L. S. L. P., E. P., M. G., F. B. and P. H. were described in considerable detail in a previous publication (Rodaniche, End C.; Kirsner, J. B., and Palmer, W. L. Lymphogranuloma Venereum in Relation to Chronic Ulcerative Colitis, J. A. M. A. 175 515-519 (Aug. 17) 1940). Further information regarding E. S. is included with the case reports appended to this article.

† Died; see text and case summary.

‡ Commercial antigen

(Palmer, W. L.; Kirsner, J. B., and Rodaniche, E. C.; J. A. M. A.)

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Fig. 5—Lymphogranuloma inguinale. Same patient as Fig. 4.

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						Source of Biopsy Specimen	Result
1. L. P.	Q	40 Positive	Reddened granular mucosa; stricture 4.5 cm. above anus	10	Strongly positive	Ulcerated mucosa below stricture	Negative
2. L. P.	♂	40 Positive	Friable, bleeding mucosa; colostomy, rectal stricture	8	Positive	Same, 5 mo. later	Positive
3. L. P.	Q	38 Positive	No inflammation; smooth stricture 6.5 cm. above anus	12	Very strongly positive	Lower margin of stricture...	Negative
4. L. C.	Q	33 Positive	Inflamed, bleeding, polypoid mucosa, stenosis of anus	13	Strongly positive	Lower margin of stricture...	Positive
5. G. R.	Q	26 Positive	Stricture 5 cm. above anus, mucosa below chronically inflamed	9	Strongly positive	Polypoid area of mucosa...	Positive
6. M. G.	Q	28 Positive	Granular, bleeding mucosa; mucopurulent exudate, no stricture	12	Strongly positive	Lower margin of stricture...	Negative
7. F. B.	♂	39 Negative	Numerous superficial ulcerations with bleeding; no stricture	11	Positive	Same, 2½ mo. later	Positive
8. B. S.†	Q	40 Negative	Granular, bleeding mucosa; no stricture	7	Positive	Rectal mucosa...	Negative
9. C. C.	♂	41 Negative	Inflamed, friable, edematous bleeding mucosa; profuse purulent exudate; no stricture	5	Positive	Same, 3 mo. later	Negative
10. P. H.	Q	50 Negative	Bleeding mucosa; benign polyps; stricture 8 cm. above anus; colostomy	8	Positive	Same, 4 mo. later	Negative
				7	Positive	Rectal mucosa...	Negative
				7	Positive	Rectal mucosa...	Positive
				0†	Positive	Mucosa below stricture...	Negative
				7	Positive	Same, 13 mo. later...	Unsatisfactory

*The cases of E. S., L. P., E. P., M. G., F. B. and P. H. were described in considerable detail in a previous publication (Rodaniche, End C.; Kirsner, J. B., and Palmer, W. L., *Lymphogranuloma Venereum in Relation to Chronic Ulcerative Colitis*, J. A. M. A. 175 315-319 (Aug. 17) 1940). Further information regarding E. S. is included with the case reports appended to this article.

† Died, see text and case summary.

‡ Commercial antigen.

(Palmer, W. L.; Kirsner, J. B., and Rodaniche, E. C.; J. A. M. A.)

TABLE 2—SUMMARY OF PATIENT'S CASE HISTORY

Date	Therapy	Virus Isolation	Rectum
1919 (bubo) 1929-1939...			Bleeding and stricture continuously present
1937 May 1939... June 6, 1939... Nov. 10, 1939. Nov. 10-20...		0	Cessation of bleeding
Dec. 24-Dec 2	Sulfanilamide, 4 Gm. daily Azosulfamide, 3.3 Gm. daily		Gradual subsidence of inflammation, one or two formed stools daily, no bleeding
Nov. 1939- Mar. 1940			Mild inflammation of rectal mucosa; stricture still present
March 1940 (conception) April 1940 July 1940		+	No recurrence of bleeding, mucosa normal, slight atrophic stricture
Dec. 1940 (de- nigrant's negative May 1941		+	

(Palmer, W. L., Kirsner, J. B., and Rodaniche, E. C. J. A. M. A.)

A more recent report is by Palmer, Kirsner, and Rodaniche.² In a series of 76 patients, with chronic inflammatory disease of the rectum, sigmoid, or colon, 43 were found to have lymphogranuloma venereum. All were white, seven were females and three were males.

In many respects, say these authors, the most interesting of our group is patient L. S. (table 2), from whose rectal mucosa the virus was recovered 21 years after the bubo and

TABLE 3—SUMMARY OF C. C.'s CASE HISTORY

Date	Therapy	Ferr Reaction	Virus Isolation	Rectum
10/1/40	.	+	.	Edematous, friable, bleed- ing, purulent discharge
10/22	+	Unchanged
10/31 to 11/19	Sulfanilamide, 2 4 to 3 5 Gm. daily	..	/	
11/19	.	..		Mucosa entirely normal
11/20-30	.	+		
11/26	.	..		Friable, bleeding; mucopur- ulent exudate
12/1-6	Sulfanilamide, retention enema daily, 2 4 Gm. in 250 cc. of water	✓	.	
12/7-4/8	Sulfanilamide retention enema 3 times weekly		..	
1/7/41	Sulfanilamide retention enema 3 times weekly			Definitely better, slight bleeding, mucosa no longer friable
2/3	Sulfanilamide retention enema 3 times weekly			Almost normal; few scat- tered areas of bleeding, no exudate
3/4	Sulfanilamide retention enema 3 times weekly	+	.	Practically normal
4/1	Sulfanilamide retention enema 3 times weekly	(Lygranum)	0	Slightly granular, practical- ly normal
4/8	Sulfanilamide discontinued			
4/29	.	.	0	Several small bleeding areas but rectum practically nor- mal

W. L.; Kirsner, J. B., and Rodaniche, E. C.: *J. A. M. A.*)

disease is known to have been present for 11 years. To our surprise, the rectal inflammation subsided entirely and the stricture disappeared almost completely after (1) sulfanilamide and azosulfamide and (2) pregnancy, an event which in itself, occurring after 20 years of sterility, was somewhat surprising. The

TABLE 4—SUMMARY OF G. R.'s CASE HISTORY

<i>Date</i>	<i>Therapy</i>	<i>Frei Reaction</i>	<i>Virus Isolation</i>	<i>Rectum</i>
11/19/40	.	+	0	Chronic inflammation with stricture 5 cm. above anus
2/4/41	.	.	+	Unchanged
3/4	.	+		Unchanged
		(Lygranum)		
3/9-20	Sulfanilylguanidine, 10 Gm. daily	.	.	
3/18	.	.		Little change
3/24	Sulfanilylguanidine, 10 Gm. daily resumed			
3/27	Sulfanilylguanidine, 10 Gm. daily continued			Unchanged
4/8	Sulfanilylguanidine, 10 Gm. daily, continued	+	0	Mucosa bleeding, stricture unchanged
4/22	Sulfanilylguanidine, 10 Gm. daily, continued		0	Less bleeding; slightly improved
5/6	Sulfanilylguanidine, 10 Gm. daily, continued		0	Unchanged
5/13	Sulfanilylguanidine, 10 Gm. daily, continued		0	No bleeding; definitely better but stricture unchanged
6/2	Sulfanilylguanidine, discontinued			

(Palmer, W. L., Kirsner, J. B., and Rodaniche, E. C.: *J. A. M. A.*)

improvement appeared to have been initiated by the chemotherapy and to have been furthered enormously by the pregnancy.

In patient C. C. (table 3) the administration of sulfanilamide for 20 days seemed to produce a most striking transformation in the proctoscopic appearance. The disease process recurred, however, within a week after the discontinuance of the drug. The use of sulfanilamide retention enemas daily for six days followed by such enemas three times weekly for four months apparently resulted in complete healing of the proctitis. The disease has not recurred as yet after seven weeks.

In contrast to the first two patients, patient M. G., whose disease was of three years' duration and was unaccompanied by stricture formation, exhibited only slight improvement after the administration of 4 Gm. of sulfanilamide daily for two weeks and no improvement after receiving 3.3 Gm. of azosulfamide daily for 27 days, followed by 5.3 Gm. daily for 14 days.

To another patient, G. R. (table 4), whose disease had been present for six years and had resulted in severe stricture formation, sulfanilylguanidine was administered almost continuously for more than two and one-half months in a dose of 10 Gm. daily. Improvement occurred slowly but nevertheless definitely. There was a gain in weight amounting to 5 kg. (11 pounds). The rectal pain disappeared. The number of stools decreased from 15 to 30 daily to two to eight daily. The bloody rectal discharge disappeared. The stricture remained about 4 mm. in diameter, but it seemed softer. The adjacent rectal wall became thin and pliable. The mucosa at the site of the stricture and below remained granular and bled easily. The bacterial count per Gram of feces decreased from an average of 20 to 50 million organisms, predominantly gram-negative bacilli, to an average of 100 to 600 thousand, predominantly gram-positive cocci.

Canizares and Morris³ treated six patients with sulfaguanidine in a daily dosage of 24 Gm., divided into four equal doses. Length of treatment varied from 27 to 47 days. All the patients with simple inflammatory proctitis experienced subjective and objective improvement, but those with narrow fibrotic stricture of the rectum showed no improvement. These authors stated that chemotherapy will do no more than heal erosions and ulcerations.

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MASTOIDITIS

Also see page 148

It is entirely feasible to close a mastoid wound without drainage if the cavity is filled with sulfanilamide or sulfathiazole, according to Livingston.¹ The author cites 13 cases in which he followed this procedure with good results.

CASE 1—A. M., a six-year-old boy, was admitted April 10, 1941, with a history that indicated right acute otitis media of four weeks' duration following measles. Mastoid swelling had been present three weeks. The ear did not drain at any time. Examination showed a large fluctuant subperiosteal abscess of the right mastoid. The tympanic membrane was thickened, slightly full, and dusky red. The temperature was normal. The leukocyte count was 17,600, with 82 per cent polymorphonuclears. On April 11 mastoidectomy was done, the abscess was evacuated, and extensive cellular necrosis was encountered. The mastoid cavity was filled with 2 Gm. of sulfanilamide and the wound was sutured without drainage. On the following day the blood sulfanilamide level was 0.8 mg. per 100 cc. Mastoid culture showed *Streptococcus hemolyticus*. At this time sulfanilamide was started by mouth at a dosage of 4 Gm. (60 grains) daily in six divided doses and was continued for five days. On April 14 the blood level was 5.6 mg. per 100 cc. The wound at this time was clean and healthy, and it was remarkable for the absence of soft tissue reaction. There was a scanty amount of bloody drainage from the incision. The ear remained dry. The leukocytes numbered 8400, with 64 per cent polymorphonuclears. Sutures were removed on April 16, when the wound was found to be completely and solidly healed.

CASE 2—C. S., a 15-month-old girl, was admitted on May 6, 1941, with a history of cervical adenitis and fever that began three weeks earlier. The date of onset of otitis media was not known. Three days before admission, swelling appeared behind the right ear. Examination showed a large fluctuant swelling over the right mastoid, temporal, and zygomatic regions. The

drum membrane was inflamed and bulging. There was no drainage from the ear. The temperature was 102.8° F. The leukocytes numbered 14,100. Sulfanilamide was started by mouth, 2 Gm. (30 grains) daily, in six divided doses. The following day at operation a large abscess was evacuated. The mastoid was cellular, moderately broken down, and filled with pus and granulations. The dura of the middle fossa was found exposed and covered with granulations. Sulfanilamide, 1 Gm., was placed in the cavity, and the wound was sutured without drainage. Culture revealed *Streptococcus hemolyticus*. For the next 11 days the course was afebrile, with gradual diminution of swelling, and a clean wound which healed by primary union. On May 12 the leukocyte count was 6200. At this time sulfanilamide was reduced to 1.3 Gm. (20 grains) daily and was stopped on May 16. On May 18 the temperature rose to 101.2° F., the leukocytes increased to 16,450, and the mastoid became swollen. On the following day the wound opened at one point and drained a clear, serous fluid. Sulfanilamide was again given by mouth, 20 grains daily. The temperature returned to normal. Drainage ceased May 24, when sulfanilamide was stopped. On June 7 there was again scanty serous drainage but no fever. Thereafter the wound remained dry and firmly healed.

CASE 3—L. S., a three-year-old boy, admitted on May 9, 1941, had had scarlet fever a month previously, followed by a throat abscess, which was incised and drained. After seeming well for ten days he complained of left earache on May 5 and had a temperature of 103° F. The pain and fever persisted. There was tympanic rupture on May 8. On the morning of admission he had a generalized convulsion with weakness of the right arm and leg. The left ear was draining freely. The left mastoid was moderately tender. The boy was very irritable. The temperature was 102.2° F. The leukocyte count was 9000. Sulfanilamide was started, 30 grains daily in six divided doses. Spinal puncture yielded clear fluid under increased pressure with 17 cells, Pandey negative, and sugar 87 mg. per 100 cc. The smear and culture were negative. Ear culture showed *Streptococcus hemolyticus*

and *Staphylococcus albus hemolyticus*. On the following day sulfathiazole 1.5 Gm. (23 grains) daily was added to the sulfanilamide dosage. The temperature ranged between 99° and 101° F. Pain and irritability had disappeared. The ear continued to drain and the mastoid remained tender. The daily peak of fever did not exceed 101.6° F. On May 12 sulfanilamide was stopped, and sulfathiazole was increased to 2.3 Gm. (35 grains) daily. On May 14 swelling of the mastoid was first noted. On May 15 sulfathiazole was stopped and operation was done on the left mastoid. A subperiosteal abscess was evacuated. The mastoid was cellular, with early softening and considerable pus under pressure. The sigmoid sinus plate was found dehiscant by necrosis, and the sinus wall was white, thickened, and bathed in pus. The cavity was filled with sulfathiazole 4 Gm. and the wound was sutured without drainage. Culture of the mastoid yielded *Streptococcus hemolyticus*. The postoperative temperature ranged from normal to 101.6° F. for two days, then remained normal for four days, then rose to 100.6° F. on May 20, 101.4° F. on May 21, 102° F. on May 22, and 100.8° F. on May 23, and remained normal continuously thereafter. On the day after operation the dressings were found soaked with a serosanguineous discharge. The wound appeared clean and healthy. Drainage was from the wound and ear. It was thin, clear, and slightly blood tinged. This drainage diminished gradually and ceased on the fifth day, when the sutures were removed. Sulfanilamide 30 grains daily was given during the febrile period from May 20 to May 22. The patient was discharged on May 24 with the wound completely healed and dry, the ear dry, and the temperature normal.

CASE 4—J. P., a four-year-old girl, was admitted on May 22, 1941, with a history of measles and pain in the left ear ten weeks earlier. There was no drainage, and the pain subsided in a few days. A month later pain in the left ear recurred, with spontaneous rupture, followed by continuous drainage until admission. Examination showed a profuse purulent discharge from the left ear and tenderness over the mastoid, with periosteal

thickening. The temperature was normal. The leukocyte count was 15,600. Sulfathiazole was given on the first day, but was stopped on the following day, when ear culture showed *Streptococcus hemolyticus*. Sulfanilamide was given 30 grains daily in six divided doses until June 7. On May 24 the temperature rose to 101° F., on May 25 it was 100.2° F., on May 26 it was 101° F. Mastoid operation on May 26 disclosed a cortical fistula and nearly complete necrosis of all cells. The sigmoid sinus and dura of the middle fossa were found exposed and covered by thick granulations. Sulfanilamide 2 Gm. was placed in the cavity, and the wound was sutured without drainage. The entire postoperative course was afebrile. At dressing on the first day a large amount of thin, bloody fluid was found oozing through the incision and from the ear canal. This diminished rapidly and was practically dry on May 30. Sutures were removed on the next day, when the wound was seen to be dry and firmly healed. Scanty serous drainage from the ear continued until June 10. There has been none since.

CASE 5—J. G., a six-year-old girl, admitted on May 22, 1941, had had measles two months previously, followed by chicken-pox two weeks later, when bilateral earache appeared, with spontaneous rupture. The left ear drained for three weeks; the right continued until admission. Right mastoid swelling appeared on May 21. Examination revealed profuse purulent drainage from the right ear and slight swelling over the right mastoid. The temperature was 101.2° F. The leukocytes numbered 14,900. Sulfathiazole was started, but was changed to sulfanilamide 3.25 Gm. (50 grains) daily, when on the following day culture showed *Streptococcus hemolyticus*. The temperature became normal. Operation on the right mastoid on May 26 disclosed a subperiosteal abscess, extensive cellular necrosis, and a perisinial abscess. Sulfanilamide 2 Gm. was placed in the cavity, and the wound was sutured without drainage. Mastoid culture yielded *Streptococcus hemolyticus*. On the first postoperative day the dressings were soaked with a large amount of blood-tinged serous fluid. This came from both the wound

and the ear. The mastoid was greatly swollen by a large hematoma. The swelling and drainage diminished progressively. The sutures were removed on May 31. At this time the temperature rose to 102.3° F. and a generalized eruption was seen. Since this was recognized as a toxic drug reaction, sulfanilamide was stopped. The temperature was normal the next day. On June 4 the wound was dry and healed, and all swelling had disappeared. There was no discharge from the ear.

CASE 6—B. K., a six-year-old boy, was admitted on May 24, 1911, with a history of a discharge from the right ear for three weeks and a mastoid swelling for ten days. Examination showed a fluctuant, tender swelling over the right mastoid and profuse purulent drainage from the right ear. The temperature was normal. The leukocyte count was 15,100. At operation on May 26 a large subperiosteal abscess was evacuated and a necrotic cellular mastoid was found. Sulfanilamide 2 Gm. was placed in the cavity, and the wound was sutured without drainage. Ear and mastoid cultures showed *Streptococcus hemolyticus*. The entire course was afebrile. Sulfanilamide was given by mouth, 40 grains daily, in divided doses, beginning on May 27, for four days. There was a considerable amount of serosanguineous drainage from the wound and ear, which decreased progressively. The wound was healed and dry on May 31. There was scanty bloody discharge from the ear, which ceased two days later.

CASE 7—A. S., a four-year-old boy, admitted May 28, 1911, had been sick for four days with a cold, fever, and cervical adenitis. He had a convulsion on the day of admission. The left ear was then draining profusely. The right drum membrane was inflamed and slightly full. The temperature was 101.2° F. The leukocyte count was 12,250. Sulfanilamide was started, 40 grains daily in four divided doses. The temperature continued to rise to about 101° F. daily. Right myringotomy on May 31 yielded pus, which drained for four days. The left ear continued to drain profusely. Sulfanilamide was reduced to 30 grains daily on June 3 and was stopped on June 5. There was about 1° elevation of temperature from June 3 to June 7. Sulfanilamide

40 grains daily was resumed on June 7 and continued until June 14. During this period there was no fever. Roentgenograms showed a well pneumatized, normal mastoid on the right side. The left showed extensive coalescence. Ear culture yielded *Streptococcus hemolyticus*. On June 14 the left mastoid became tender. On June 16 left mastoidectomy was done. The entire mastoid was necrotic. The cavity was filled with sulfanilamide 2.5 Gm. and the wound sutured without drainage. Mastoid culture showed *Streptococcus hemolyticus*. On June 17 the blood sulfanilamide level was 1.5 mg. per 100 cc. There was a great deal of serosanguineous drainage from the wound and ear, which diminished only slightly during the next ten days. During this period the patient was afebrile. On June 27 the temperature rose to 103.2° F., the mastoid became swollen and tender, and the ear discharge was frankly purulent. On the following day two fistulas appeared in the wound, draining pus. Daily sulfanilamide irrigations through the upper fistula were started according to the method described by Herrell and Brown. This consists of a suspension of 2 Gm. of sulfanilamide in 100 cc. of aqueous 0.8 per cent solution of sulfanilamide. Little if any of the crystals left the syringe, however, so one must assume that the fluid contained only 0.8 per cent of the drug. From this time on the temperature remained normal. Drainage from the wound and ear diminished slowly. The wound was healed and dry on July 18. The ear was dry two days later. This is the only case of this series in which purulent drainage occurred after operation.

CASE 8—A. H., a six-year-old girl, who was admitted June 4, 1941, had had several attacks of bilateral acute suppurative otitis media in the past six months, which had resolved without complications. The present sickness began three weeks previously with a cold, pain in the left ear, and spontaneous rupture. Mastoid swelling appeared a week later. Ear drainage stopped three days before admission. Examination showed a subperiosteal abscess over the left mastoid and zygoma. The drum membrane was red and bulging, but there was no discharge. The temperature was 100.4° F. The leukocyte count was 10,300. On June 6,

at operation, a large subperiosteal abscess was drained. The mastoid was cellular and extensively necrotic. Sulfanilamide 4 Gm. was placed in the cavity, and the wound was sutured without drainage. Culture showed *Streptococcus hemolyticus*. No sulfanilamide was given by mouth at any time. The sulfanilamide blood level on the day after operation was 4.7 mg. per 100 cc. On the third day it was 0.95 mg. The entire postoperative course was afebrile. There was profuse serosanguineous drainage from the wound and ear, which diminished progressively. On June 14 all swelling had disappeared, the wound was dry and healed, and the ear had stopped draining.

CASE 9—A. T., a seven-year-old girl, admitted on June 11, 1941, had had suppuration of the right ear, with scarlet fever two years previously. At that time a subperiosteal abscess had been drained without mastoidectomy. The ear has drained intermittently since. Six weeks before admission, following a cold, the ear began to drain profusely and swelling appeared in front of the ear. This subsided in a few days, but reappeared three days before admission. Examination showed a tender, nonfluctuant swelling over the right zygoma. There was scanty purulent drainage from the ear through a large central perforation of the pars tensa. The temperature was 101.2° F. The leukocyte count was 12,200. During the next two days the swelling spread to the temporal and mastoid regions and became fluctuant. At operation on June 14 a large subperiosteal mastoid and zygomatic abscess was evacuated. The bone showed advanced necrosis throughout. There was no evidence of previous mastoid surgery. No cholesteatoma was found. Sulfathiazole 3 Gm. was placed in the cavity and the wound was sutured without drainage. Culture yielded *Streptococcus hemolyticus*. There was considerable drainage of bloody serous fluid from the wound and ear for two days. This then diminished rapidly. On June 23 the wound was healed. Scanty serous drainage continued from the ear for eight days. The entire course was afebrile.

CASE 10—N. C., an eight-year-old girl, admitted on June 29, 1941, had had chickenpox five weeks previously, followed by

measles. The right ear ruptured spontaneously three weeks before admission. The patient then had a high fever and was given sulfathiazole for one week, when the temperature became normal, remaining so until two days before admission, when it rose to 102° F. The ear discharged profusely throughout. On admission, the right mastoid was quite tender. Roentgenograms showed a large-celled mastoid with signs of early coalescence. The temperature was 102.6° F. The leukocyte count was 14,800. The temperature rose to 101° F. daily until July 2, when right mastoidectomy was done. Extensive necrosis was found. Sulfathiazole 2.5 Gm. was placed in the cavity and the wound was sutured without drainage. *Streptococcus hemolyticus* and *Staphylococcus aureus* were found in cultures of the aural discharge. Culture of the mastoid pus showed the streptococcus alone. The temperature rose to 101.6° F. on the first postoperative day to 100.8° F. on the second and then returned to normal. There was moderate blood-tinged serous drainage from the wound and ear. The wound was dry on the fourth day. On the seventh the temperature was 101° F. A small quantity of serous drainage issued from the lower end of the incision. The rest of the course was afebrile. The ear remained dry. The wound was dry and firmly healed two days later and has remained so.

CASE 11—E. C., a 3½-year-old boy, was admitted on July 2, 1941, with a history of pain in the left ear one week previously and spontaneous rupture on the same day. Mastoid swelling appeared four days later. Examination showed a fluctuant swelling over the left mastoid and profuse purulent aural discharge. The temperature was normal. The leukocyte count was 15,400. Sulfathiazole 30 grains daily was given from July 2 to July 4. At operation on July 4 a subperiosteal abscess was evacuated. The mastoid was small celled with scanty necrosis. The lateral sinus was found exposed 1 cm. below the knee and was covered with thick granulations. Further exposure to the normal sinus wall showed the granulations to extend 4 cm. posterior to the knee. Sulfathiazole 2 Gm. was placed in the cavity and over

the exposed sinus. The wound was sutured without drainage. Cultures of pus from the ear and mastoid yielded pneumococcus type 1. Since the extensive sinusal granulations did not seem compatible with an ear infection that had begun only a week earlier, the parents were questioned as to previous ear infection. It was then learned that the child had had measles in March, with left earache for a few days, but no drainage. It was assumed, therefore, that the first attack of otitis media initiated the perisinial invasion. The postoperative course was afebrile. There was scanty blood-tinged serous drainage from the wound and the ear for three days. The sutures were removed on the fourth day, when the patient was discharged with the wound healed and the ear dry.

CASE 12—M. K., a three-year-old girl, was admitted on July 2, 1941, with a history of right otorrhea for two weeks and mastoid swelling for three days. Examination showed a fluctuant swelling over the right mastoid and zygoma and profuse purulent drainage from the ear. The temperature was normal. The leukocyte count was 14,700.. Sulfathiazole was given, 30 grains daily for two days. At operation on July 4 a zygomatic mastoid abscess was drained and moderately advanced necrosis of the cells was found. Sulfathiazole 2 Gm. was placed in the cavity and the wound was sutured without drainage. Cultures of pus from the ear and mastoid produced *Streptococcus hemolyticus*. The postoperative course was afebrile. There was scanty ear and wound drainage for three days. The sutures were removed on the fourth day, when the wound was found healed and the ear dry.

CASE 13—L. R., a 17-month-old girl, was admitted on July 5, 1941, with a history of right ear discharge for two and one-half weeks. Mastoid swelling appeared two days before admission. Examination showed a fluctuant swelling over the right mastoid and profuse purulent aural discharge. The temperature was normal. The leukocytes numbered 6100. At operation on July 7 a subperiosteal abscess was drained and necrotic cells were exenterated. Sulfanilamide 2 Gm. was placed in the cavity and the

wound was sutured without drainage. Cultures of the mastoid pus yielded *Streptococcus hemolyticus*. The postoperative course was afebrile. There was moderate bloody drainage from the wound and ear for three days. Sutures were removed on the fifth day, when the ear was dry. There was a 1 cm. separation of the skin margins at the middle of the wound, but no drainage. The wound was completely healed on the eighth day.

REFERENCE

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MENINGITIS

See page 132



MENINGOCOCCIC INFECTIONS

Lepper, Sweet, and Dowling¹ report on the use of sulfadiazine and sulfamerazine in 118 cases of meningococcic infections. Sulfadiazine was the mainstay of treatment in 96 cases with ten deaths. One-half of these deaths occurred within the first 24 hours after admission. Eight of these patients received serum in addition. Twenty-two cases were treated with sulfamerazine with two deaths, neither dying within 24 hours. Three cases in this group received serum in addition to the sulfamerazine.

The response to therapy in the sulfadiazine cases in which survival occurred has varied from dramatic to satisfactory. The time taken for the patient to become rational and the temperature to become normal has been spread over a wide range, the extremes being 0.25 to 6.75 and 0.0 to 12.0 days and the averages 0.48 and 2.7 days respectively.

The most significant complications of sulfadiazine therapy as well as the commonest have been urinary in nature. The criteria which we recognize as diagnostic of urinary lithiasis are renal colic, gross hematuria, and pronounced unexplained oliguria or anuria with or without azotemia or any combination

TABLE 1—SEVERITY OF ILLNESS AND RESULTS OF TREATMENT OF MENINGOCOCCIC MENINGITIS TREATED WITH SULFADIAZINE AND SULFAMERAZINE

Treatment	Number of Patients	Severity of Illness					
		Admitted in Coma		Dextrose Less Than 10 mg. per 100 cc		Many Cocci in Initial Spinal Fluid	
		Number	Per cent	Number	Per cent	Number	Per cent
Sulfadiazine in series	22	7	31.7	13	59.2	7	31.7
Sulfamerazine in series	22	6	27.3	12	54.5	5	22.7
Sulfadiazine, all cases	96	38	39.6	28	47.6†	37	39.4‡
Total of lines 2 and 3	118	44	37.3	40	48.7§	42	36.8¶

Treatment	Results of Treatment					
	Died		Recovered			Specific Serum Used
	Number	Per cent	Average Duration of Coma	Average Duration of Fever*	Average Duration of Pleocytosis	
Sulfadiazine in series	2	9.1	0.66	3.0	28.0	1
Sulfamerazine in series	2	9.1	0.28	2.9	22.9	3
Sulfadiazine, all cases	10	10.4	0.48	2.7	20.6	8
Total of lines 2 and 3	12	10.2	0.44	2.8	21.0	11

*Temperatures permanently below 101° F. by rectum. †Determined in only 60 patients. ‡Determined in only 82 patients. §Based on 94 patients. ¶Based on 114 patients.

of these. There have been ten cases presenting one or more of these findings. In six of these cases symptoms developed at a time at which the drug could be discontinued safely. In all six cases an uneventful subsidence of symptoms occurred when this was done and fluids were forced. In cases in which further treatment of the infection was required the sulfonamide dosage was maintained, decreased, or temporarily interrupted, depending on the blood sulfadiazine level. Fluids were forced and attempts at alkalization were made with prompt and satisfactory recovery from renal symptoms. In only one case was cystoscopy needed. This was done on the third day of therapy and the drug was reinstituted in low dosage after a 24-hour interval.

TABLE 2—RELATIONSHIP OF THE DATE OF ONSET TO SEVERITY OF ILLNESS AND PROGNOSIS

Date of Onset	Number of Patients	Admitted in Coma		Died		Average Duration of Coma*	Average Duration of Fever†	Average Duration of Pleocytosis
		Number	Per cent	Number	Per cent			
Jan. 1, 1942 to June 30, 1942	28	3	10.7	8	28.6	0.24	1.67	14.7
July 1, 1942 to Dec. 31, 1942	22	3	13.6	10	45.4	0.75	3.05	20.4
Jan. 1, 1943 to May 31, 1943	67	6	8.5	31	46.4	0.86	3.44	25.3

*Includes only patients who recovered after treatment with sulfadiazine.
†Temperatures permanently below 101° F. by rectum.

Other toxicities from sulfadiazine have included three instances of rash with fever, two instances of fever alone, and one instance of rash and conjunctivitis. One patient developed a transient leukopenia.

In addition to the foregoing patients, since March, 1943, an attempt has been made to evaluate sulfamerazine by giving alternate patients this drug and sulfadiazine. To date this study is unfinished but, as seen in table 1, 22 cases have been treated with each drug with two (9.1 per cent) deaths in each series. The age distribution was approximately the same in the two groups. The severity of cases as measured by presence of coma, dextrose content of the fluid on admission, and the number of organisms in the initial smear showed that those patients who received sulfadiazine were slightly more ill. The somewhat more rapid response in patients who survived after receiving sulfamerazine may be correlated with their being less seriously ill. Only one person in the sulfadiazine group received serum. Three sulfamerazine-treated patients have also received serum.

Three sulfamerazine-treated patients had kidney complications as defined. One required cystoscopy. The others responded favorably to conservative treatment. Two instances of rash and fever, two examples of fever alone, and one instance of leukopenia have occurred with sulfamerazine.

Serum: As shown in table 1, 11 patients received serum. The only patient in the entire series who received serum intraspinally did so in another hospital immediately after the diagnosis. One other patient also received serum before admission. The course of these two patients was not different from the course of those who received no serum. One patient who was in diabetic acidosis was given serum as soon as the initial dose of sodium sulfadiazine was completed. However, the patient died within eight hours. Eight other patients received serum after having failed to respond to sulfonamide therapy in the first 24 to 48 hours. Four of these continued to fail and died. Four of these patients survived. In two it was felt that the recovery was definitely related to the administration of the serum in that a prompt improvement followed. In the other patients who recovered, the actual value of the part played by the serum in influencing the outcome is questionable. Four of the six surviving patients developed mild serum sickness.

Of the three cases of meningococcemia without evidence of meningitis, one presented an acute onset of petechial rash and high fever and the other two showed a maculopapular rash, joint pains, and fever. The first patient was treated with sulfadiazine with rapid subsidence of symptoms and no complication. The other two patients had recovered spontaneously by the time the diagnosis was established. They were observed for a prolonged period and were discharged in good condition.

Table 2 shows the effect of time of onset of the diseases as the epidemic progressed on the incidence, severity, and recovery. From January 1, 1942, to June 30, 1942, there were 28 patients; from July 1, 1942, to December 31, 1942, there were 22 patients, and from January 1, 1943, to May 31, 1943, there were 67 patients.

In the first time interval there were three (10.7 per cent) deaths, in the second interval three (13.6 per cent) deaths, and in the third period six (8.5 per cent) deaths. It is seen, therefore, that no significant increase or decrease in mortality has occurred. On the other hand, the average duration of coma after treatment

and of average time taken for temperature and cell count to return to the standards used have shown a prolongation in the more recent cases. The average duration of coma for the last two periods are both significantly greater than that for the initial interval, but the difference between these two compared with each other is not. The same statistical relationship holds for the average times for the temperature to return below 101° F. and the cell count to return below 30 cells per cubic millimeter. There has also been an increase in the percentage of patients admitted in coma. In the first six months eight (28.6 per cent) patients were admitted in coma. In the next six months there were ten (43.4 per cent) patients and in the last five months 31 (46.4 per cent).

REFERENCE

1. LEPPER, MARK H.; SWEET, LEWIS K., AND DOWLING, HARRY F.: J. A. M. A. 123:134 (Sept. 18) 1943.



MILITARY MEDICINE

The lessons that have been learned from civilian use of sulfanilamide during the past few years have not been lost as far as military medicine is concerned, says Matuska,¹ and the armies of the world are using sulfanilamide powder and tablets as a part of the first-aid equipment of the individual soldier. The wounded soldier himself is being trained to open the package of sulfanilamide and pour it into the open wound. For penetrating wounds it has been suggested that a sulfanilamide pencil be devised, that could be thrust into the punctured track made by a bullet. If the soldier is unable to do so, it can be done by the litter bearer or a nearby companion. Sulfanilamide has been the drug of choice, as it does not tend to cake as do some of the other sulfonamides when sprinkled into a wound or into a serous cavity.

In previous wars greater numbers of men lost their lives as a result of disease than as a result of bullets. It is likely that this will be the first war in which more men will be killed by bullets

that one can see than by bacteria that one cannot see with the unaided eye, and this difference may in a large degree be the result of the use of sulfonamides.

Dysentery has always been the cause of many deaths in previous wars, and it is also a disease to be reckoned with in this war, due to difficulty with water supply and other problems that are a result of the mobility of modern warfare, and the rapid advances (and in some cases the rapid retreats which we hope are now at an end). However, chemotherapy with one of the sulfonamides, in this case sulfaguanidine, has completely revolutionized the treatment and prognosis of bacillary dysentery. Sulfaguanidine appears to be quite as effective in the treatment of bacillary dysentery, according to a report by Lyon, as sulfanilamide is in the treatment of some streptococcal infections, or as effective as sulfathiazole is in pneumococcal infections. Sulfaguanidine seems to be equally effective against all strains of the various kinds of bacillary dysentery, and most striking results have been seen in cases of Shiga and Flexner bacillus strains. One may well suppose, in view of this, that sulfaguanidine may become important in this war, possibly in its use in extensive abdominal injuries sustained in battle.

In the treatment of surgical and orthopedic conditions occurring as a result of battles or bombs, the sulfonamides seem to be at least one answer to the surgeon's prayer. Experience gained from the casualties which occurred during the raid on Pearl Harbor revealed acutely injured patients, treated under pressure, by a small group of American-trained surgeons, in a small space, in a brief time, with excellent results. The lessons learned fortified the previous opinion of many surgeons, and others have been helped to learn that there are now available certain adjuncts to therapy of the greatest value which, if widely used, *will do much to reduce morbidity and mortality of a wide variety of battle casualties.*

At Pearl Harbor, Long reports that amputation stumps were seen that were made in a hurry by the guillotine method, and the end frosted over with sulfanilamide crystals, and then covered

over with vaseline gauze. Seven weeks later one case was draining serum, all the others had healed completely and were tightly closed. Nine weeks after injury the stumps were ready for an artificial prosthesis. In our mind's eye we can compare that with the last war, where there were periods of protracted suppuration from the amputation stumps, with long physical disability with its resultant mental strain, before the stump was ready for an artificial limb. Parenthetically, it was interesting to note at Pearl Harbor that even though large amounts of sulfonamides were used locally and by mouth toxic reactions were rare, and only one case of probable drug fever was seen. Even though a serious toxicity is infrequent, it is nevertheless advisable that the medical officer be on the alert for the warning signs of a possible sulfonamide intoxication, such as a sustained fever after a period of normal temperature, decreased white count with decreased polys, skin eruption, and the like.

At the Naval Hospital at Pearl Harbor the majority of the compound fractures that were seen were found to involve the tibia or fibula or both. These were thoroughly cleansed, débrided, fractures reduced, wounds sprinkled with crystalline sulfanilamide, covered with vaseline gauze, and plaster casts were applied. Sulfathiazole or sulfanilamide was given by mouth for four to ten days. It was found that infection was largely prevented, the bones in the lower leg remained in good position, and evacuation was simplified. Seven weeks later there was no evidence of osteomyelitis of the long bones, and three cases in which there was a mild infection in a joint. These achievements would not have been anticipated prior to the advent of the sulfonamides. Long suggests that prophylactic doses of two or three tablets every four hours be given in all severe cases of crushing injuries in which infection with streptococci or gas bacilli might subsequently occur.

The sulfonamides will probably also come into more general use in burn cases. The tannic acid method of treating burn cases is still favored in military medicine, because of its ease of application when there are large numbers of cases to be treated

nose and throat examination. Intranasally, the mucous membranes were chronically inflamed. Mucopus was seen in each middle meatus and on each nasal floor. The left middle turbinate was hypertrophied and boggy. X-ray examination showed a diffuse clouding of each antrum. Diagnostic lavage of each antrum gave a return of white flocculent mucus and pus. Immediately following the irrigation, her headache ceased. Were she a better risk, radical surgery would be indicated. Biweekly antrum irrigations, followed by instillations of sulfallantoin solution over a period of four weeks, have resulted in a marked decrease of pus in each sinus. Examination at this time reveals a healthier-looking mucosa. No discharge is seen and in addition the left middle turbinate appears more normal in size. Symptomatically, the headaches have entirely disappeared and there has been a lessening of postnasal discharge and cough.

CASE 2—This man has complained of nasal obstruction, postnasal discharge, irritative cough, and frequent colds. He very often suffers from dull headaches, tires easily, and lacks the stamina to carry on his work. Intranasal examination reveals a chronically inflamed mucosa. All turbinates are hypertrophied and boggy. A large amount of pus is seen on each nasal floor. X-ray examination shows a marked diffuse clouding of each maxillary sinus. Diagnostic lavage of each antrum gave a return of pus. Repeated irrigations over a period of several weeks failed to give the desired results and a bilateral intranasal antrotomy was considered. However, instillations of sulfallantoin solution have resulted in an improvement and, therefore, operative procedures are being postponed. In addition to our biweekly instillations, the patient sprays his nose with sulfallantoin twice daily.

CASE 3—This patient had an attack of acute pansinusitis of one week's duration. At the start there was a slight elevation of temperature, malaise, and headaches. The nose became completely blocked, and after several days a mucopurulent discharge developed. Examination intranasally revealed an acutely swollen mucosa bathed in mucopus. At first relief was obtained by shrinking the nasal mucosa with ephedrine and weak cocaine

solution. Later, he was given daily sinus displacement treatments with sulfallantoin solution. This resulted in a marked improvement of both subjective and objective symptoms. Treatment was continued by intranasal spraying with the drug and this resulted in complete recovery.

CASE 4—This patient had an acute exacerbation of a chronic sinusitis and vasomotor rhinitis. At this time there was a marked swelling of the nasal mucosa with a serous and mucous discharge. Nasal breathing was impossible. This condition was deemed too acute for immediate displacement therapy. The swollen mucosa was treated with a vasoconstrictor, followed by instillations of sulfallantoin solution. Improvement followed daily treatment. In this case it was difficult to decide whether relief from the acute symptoms was due to the vasoconstrictor used or to a combination of both medicaments, as vasoconstriction always improves vasomotor swellings.

CASE 5—This patient complained of pain in her left cheek, left-sided headaches, and a profuse nasal discharge, chiefly on the left side, following an acute cold. Intranasal examination on the left side showed an inflamed and swollen mucosa. Mucopus was seen in the middle meatus and nasal floor. X-ray examination revealed a diffuse clouding of the left antrum with some thickening of the lining mucosa and also a slight involvement of the right antrum. As this patient was previously treated for a similar condition, the diagnosis of an acute exacerbation was made. Sulfallantoin solution sprayed into the nose several times daily was followed by some amelioration of the symptoms. As the very acute symptoms subsided, the antrum was irrigated and sulfallantoin solution introduced directly into the sinus. This was repeated daily and after several days recovery was rapid.

CASE 6—This patient is a young child who catches frequent colds. When seen on the third day after onset, the nasal membranes were swollen and there was a serous discharge. No general medication was given. Sulfallantoin solution was instilled into the nose several times a day with the head extended. The swelling decreased, breathing was easier, and the general symptoms

soon subsided. Comparing this therapy with the methods formerly employed a shorter duration of the acute cold was noted.

CASE 7—This patient's sinus history is of many years' duration. Six years ago he had a submucous resection of his nasal septum. A year later a bilateral intranasal antrotomy was performed. He now complained of alternate nasal obstruction, postnasal discharge, and an irritative cough. Headaches and malaise were frequent. The nasal mucosa was dry and the middle turbinate hypertrophied. The antral windows were almost completely closed. Transillumination showed both antra to be dark. He was given a series of biweekly displacement treatments with sulfallantoin solution. The postnasal mucus soon became thinner and less tenacious, and later considerably lessened. The cough subsided. As the turbinates reduced in size, the breathing became easier. Following the termination of the displacement treatments, he continued to spray his nose daily with the solution.

CASE 8—This patient had an acute cold which lasted longer than usual. He developed headaches and the general feeling of malaise did not leave him. Examination of his nose revealed a red and swollen mucosa with a large amount of mucopus in each side. A diagnosis of acute sinusitis following a cold was made. He was given a series of three displacement treatments with sulfallantoin solution. This resulted in a complete disappearance of his symptoms.

CASE 9—This patient had a deviated nasal septum and a left chronic maxillary sinusitis. X-ray examination showed a thickening of the mucosa lining the left antrum with granulations. A submucous resection and a left intranasal antrotomy were performed. At the conclusion of the operation sulfallantoin powder was insufflated into the antrum. This was repeated every other day. The convalescent period was considerably shorter than usual for this type of operation. The discharge from the sinus was less than is usually seen and recovery was complete in a shorter time.

CASE 10—This patient had had intermittent attacks of bilateral maxillary sinusitis. His chief complaints had been profuse nasal discharge, thick tenacious postnasal discharge, and a dry cough. Dull headaches accompanied the attacks. Antral lavage produced white flocculent pus and seemed to result in some improvement. However, it was felt that simple irrigations were not enough and could not lead to a permanent cure. Before advising radical surgery, it was decided to give a series of treatments with sulfallantoin. Using a combination trocar-rasp in each inferior meatus, an opening into each antrum was made. This was large enough to permit the introduction of a canula through which the sinus was irrigated. Following this it was dried as thoroughly as possible by blowing in warm air. Next a eustachian catheter was placed in the sinus and sulfallantoin powder insufflated by attaching the powder blower to the catheter. Rotation of the catheter insured the deposit of the sulfallantoin powder in all parts of the sinus. Through this window powder was blown into the sinus every other day. A great improvement in the symptoms was soon noted and radical surgery has been indefinitely postponed.

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NEPHRITIS

Despite the fact that sulfonamides cause damage to the urinary tract, they have been used with benefit in patients who already have renal damage. Thus, Williams, Longcope, and Janeway¹ recommend the use of sulfanilamide in the treatment of acute glomerulonephritis. These authors claim that patients with acute nephritis treated with sulfanilamide improve much more rapidly than those not so treated. Furthermore, their incidence of recoveries was greater and the number of patients pursuing a progressive course was less in a group treated with sulfanilamide than in a control group.

Helmholz² used minimal doses of sulfonamides on a patient with marked deformity of the urinary passages and chronic urinary infection after a large dose was not tolerated. The patient was treated with sulfathiazole for infection of *Escherichia coli*. The infection was cured with doses of 0.25 Gm. six times a day, but pseudomonas infection appeared in its place and remained up to the time the article was written. However, the patient's general condition was much improved. This article shows that although an average clinical dose may not be tolerated a smaller dose may bring about improvement.

Fishberg³ believes that even in a case of previous renal damage complicated by infection, the danger from the latter may be so great that an appraisal of the risks of the primary disease and the drug administration indicates that the sulfonamide should be used. He reports a case in which sulfathiazole was administered with probably lifesaving effects to a girl with lobar pneumonia and long-standing azotemia due to chronic pyelonephritis. Renal insufficiency, he says, may modify three of the mechanisms by which sulfonamides produce untoward effects. The diminished concentration ability lessens rather than increases the risk of precipitation of the sulfonamides in the urinary passages. It may reduce the possibility of damage to the renal parenchyma by nephrotoxic agents, as such direct chemical damage was absent in the patients with renal damage who were seen by this author. Smaller amounts of the drug are needed, as high blood levels are maintained longer in patients with previous kidney trouble and resultant slower excretion.

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OPHTHALMIA NEONATORUM

See page 263

SULFONAMIDE THERAPY IN OPHTHALMOLOGY

Treatment of *staphylococcal conjunctivitis*, according to Fritsche,¹ is varied and consists of the usual antiseptics, applications of two per cent silver nitrate to the conjunctival surfaces of the lids, massage of the lids to express the meibomian glands, and use of hot compresses. In occasional cases, five per cent silver nitrate produces results when two per cent fails.

Before the advent of sulfonamides, the use of staphylococcus toxoid and vaccine was the most satisfactory treatment for stubborn cases and still should be used in severe or refractory cases, because it will cause a generalized antibody response as well as desensitize the individual to the toxin. Staphylococcus antiserum has been used with some success, but the average case hardly warrants its use. Massage of the lids in conjunction with three per cent ammoniated mercury ointment was very helpful, although more recently the sulfathiazole powder and now the ointment in five per cent strength seem preferable. Many cases respond to this dramatically, others in lesser degree, and some show no response at all. Some cases seem to show slower response to this drug during recurrences, indicating the ability of some strains to develop a tolerance to the drug. Rarely an individual may show a reaction to the drug with an exacerbation of symptoms, usually an increased inflammation of the conjunctivae and lids, with lessened discharge. This condition improves rapidly when the drug is withheld. The sulfathiazole ointment should be used frequently, up to eight times daily, and should be accompanied by gentle massage of the lids in chronic cases. Severe cases and those that have a tendency to recur should be treated with the vaccine or toxoid in increasing doses to establish an antibody titer sufficient to cure or improve the disease. Those cases which occur during the course of sties or chalazions usually respond to treatment of the primary condition. The serobacterin preparation containing both the antigen and the antibody seems, in the author's experience, to be the preparation best suited for the treatment of severe cases, especially those complicated with

keratitis or catarrhal ulcers. This preparation is marketed in the form of the combined serobacterins of several strains of staphylococci and streptococci. In milder cases the toxoid or vaccine is sufficient to build up an antibody titer and also has a foreign protein effect.

Those cases complicated by the superficial corneal epithelial defects, if painful, may be treated by closing the eye with a patch, provided the discharge is scanty and the pad is removed frequently for treatment with hot applications, cleansing, and instillation of antiseptic or sulfathiazole ointment.

Cases of catarrhal ulcer are treated as for severe uncomplicated staphylococcic conjunctivitis. In addition the ulcers should be cauterized with trichloroacetic acid or other strong antiseptic, using Gifford's corneal probe with a wisp of cotton which is sparingly dipped into the acid. Atropine or other mydriatic is instilled when indicated and can be prescribed in a cod-liver base which supplies the benefits of vitamin A locally.

Bacteriophage has been used with some success. It may cause an exacerbation of symptoms during the first day of use. The author's limited experience with it did not warrant its use in preference to the sulfathiazole or toxoid.

Scobee, in a series of 18 cases of recurrent staphylococcic conjunctivitis, had secured improvement in all cases using 1 to 5000 aqueous solution of zephiran four times daily and weekly massage of the meibomian glands.

Julianelle, Boots, and Harrison, using toxoid as sole treatment in 30 cases of staphylococcic eye infection, concluded that toxoid is not an effective method of treating presumably staphylococcic eye infections.

Only ten of their cases showed improvement during the treatment and 13 cases were asymptomatic after six months.

Presumably, a sensible approach to the treatment of staphylococcic conjunctivitis is not any one remedy for all cases, but different treatment or that combination of treatment which seems most suitable for each case. The elimination of local foci as meibomitis or infection in pseudoglands of Henle are im-

portant. Massage of the lids is helpful, especially if used in conjunction with antiseptics or sulfathiazole ointment. Probably the value of toxoid is also increased if some of the stagnating pockets of staphylococci are expressed from these glands at the time the antibody titer is rising. It is possible that dental infection may act as a sensitizing factor to the toxin in rare instances. The use of vitamin A has been claimed to cure some cases of asthenopia, and it is possible that some of these cases may have been mild cases of chronic conjunctivitis which benefited from the generally increased bodily resistance following the use of vitamin A.

Selfa² treats many eye diseases by the oral administration of sulfathiazole, using 0.03 to 0.04 Gm. per kg. of body weight for from six to nine days. This medication may be repeated, when necessary, after an interval of five days. Four patients with sties were cured by sulfathiazole in from two to four days. Two cases of acute staphylococcic conjunctivitis responded to sulfathiazole and mild protein silver in from seven to eight days. Sulfathiazole together with local remedies was effective also in four cases of chronic conjunctivitis. The action of sulfathiazole in three cases of acute dacryocystitis was not quite as prompt as that of azosulfamide. Sulfathiazole proved ineffective in two cases of fistulous dacryocystitis. In 16 cases of trachoma sulfathiazole medication was combined with local applications. There was no appreciable effect on the follicles, but the corneal lesions, the subjective symptoms, and the superimposed infection yielded rapidly. This diversity of action on the palpebral and corneal localizations of trachoma is an apparent contradiction. If the corneal ulcers are to be regarded as the result of the trachomatous follicles, it is difficult to explain why the sulfonamides act so energetically on the corneal localization. This dissociation of effect suggests two stages or types in the development of the causal organism of granular conjunctivitis. The age of the trachoma may also be a decisive factor. In ocular disorders sulfathiazole produces effects similar to those of sulfanilamide, but

in the case of a sty its action is more rapid and energetic than that of other sulfonamides.

Bellows³ states, however, that of the four most commonly used sulfonamides, sulfanilamide yields the highest concentration in the blood and ocular tissues and fluids, while much lower concentrations which are below the value accepted for chemotherapeutic effectiveness are reached by sulfathiazole and sulfadiazine. The value for sulfapyridine is between these two extremes. Therefore, under ordinary circumstances, it would appear that only sulfanilamide or sulfapyridine are capable of providing adequate concentrations in the ocular tissues and fluids. However, the concentration of sulfathiazole and sulfadiazine in the eyeball may be increased by the application of heat or mecholyl, or by paracentesis, or by inflammation resulting from infection.

Local administration of sulfonamides, says this author, has two obvious advantages: (1) Achievement of rapid, high concentration; and (2) avoidance of systemic toxic manifestations. Due partly to its greater solubility and small molecular size, sulfanilamide when applied topically reaches a concentration in the eye more than ample for chemotherapeutic effectiveness. On the other hand, the local application of sulfapyridine, sulfathiazole, and sulfadiazine produces concentrations in the aqueous humor less than half the required strength. Increases in concentration to a satisfactory level, however, can be achieved by iontophoresis. The highest concentration of sulfathiazole within the aqueous humor following local application is 1 mg. per cent. This may be increased to 10 to 20 mg. per cent with the use of a wetting agent which lowers surface tension. Such agents include bile salts, aerosol, sodium laurelate, zephiran, duponol, and oconol. The author is conducting studies to determine which of these substances is most practicable for ophthalmologic purposes.

Oral administration of sulfonamides, says Bellows, because of their toxicity should not be used indiscriminately or for every slight infection, particularly those which are self-limited or easily controlled. When infection has begun in the interior of

the eyeball or has progressed beyond the reach of topical application, oral administration seems to be indicated. However, in such conditions as *trachoma* and *gonorrheal conjunctivitis*, where local therapy might be expected to yield most effective results, clinical experience proves oral therapy to be the superior method. A combination of both oral and local administration in some instances may be the best form of therapy.

The following are the indications for sulfonamide therapy in ophthalmology given by this author:

Erysipelas: Although not primarily an ocular disease, it is of interest because of the site of predilection—the inner canthus of the eye—a factor leading to ocular complications: Lid abscess, corneal ulceration, and orbital cellulitis. Keynote of success in treating erysipelas is the early administration of sulfonamides. If given after the third day, sulfonamides appear to have no effect whatsoever on the course of the disease.

Molluscum Contagiosum: A contagious virus disease sometimes involving the eyelids, conjunctiva, and cornea. It may respond to sulfonamides. One observer has reported clinical cures in six of eight cases treated with sulfapyridine. In the other two patients the drug was discontinued because of toxic manifestations.

Gonorrheal Ophthalmia: In most cases of gonorrheal conjunctivitis, sulfonamides in sufficient dosage will free the secretion of gonococci more quickly than the use of irrigations and foreign protein alone. Sulfapyridine and sulfathiazole appear to be superior to sulfanilamide in gonococcal infection. Negative smears are obtained with sulfathiazole in one day as compared to the two days required for sulfapyridine.

Trachoma: As a general rule, virus diseases are not influenced by sulfonamides, yet there are several notable exceptions mentioned in the literature, such as trachoma, inclusion blennorrhea, lymphogranuloma venereum, and psittacosis.

While evidence is lacking that sulfonamides actually cure trachoma, most clinicians agree that there is improvement in

subjective and to a lesser degree in objective symptoms. Oral administration of sulfonamide is the generally accepted method.

Lymphogranuloma Venereum Ophthalmitis: This is rare, but whether it be conjunctivitis, keratitis, or iritis, a sufficient number of reports exist to indicate that it responds to sulfonamide therapy as rapidly in the eye as in other parts of the body.

Acute Conjunctivitis: Although most of the organisms causing this condition are admittedly sensitive to sulfonamides, the necessity for using sulfonamides locally for it is questionable. The ordinary case likewise is too mild and self-limited to require so drastic a measure as oral therapy.

However, Sulzman and Elliott⁴ used sulfathiazole locally in conjunctivitis and report cures in an average of two days against seven days in cases treated with argyrol or zinc sulfate. Their report follows:

In the use of powdered sulfathiazole locally on the acutely inflamed conjunctiva, there was considerable irritation and pain. To circumvent this, we instilled one per cent pontocaine hydrochloride. This routine usually eliminated local discomfort, although occasionally a patient would admit a slight burning sensation. Some complained of a transient blurring of vision caused by a film produced from the powder and lacrimal secretion. No other untoward reactions were found.

We soon discovered that the most practicable way of applying the powder was by the use of a small spoon, such as is used in otology for the removal of cerumen. The convex aspect of the instrument was used in spreading the powder evenly along the inferior conjunctival *cul-de-sac*.

In all, 167 cases were studied, and these were divided into two groups, as shown in table I. Cases were treated once a day, and no treatment was prescribed between visits to the dispensary. Patients were cautioned not to remove the paste formed when tears mixed with the powder, in order to maintain contact of the drug with the inflamed conjunctiva as long as possible.

From the tabulated results it will be noted that the average duration of the cases treated with powdered sulfathiazole was

TABLE I—SUMMARY OF TREATMENTS

<i>Drugs Used</i>	<i>Number of Cases</i>	<i>Average Duration (days)</i>
Argyrol or zinc sulfate	123	7
Powdered sulfathiazole	44	2

TABLE 2—OCULAR INFECTIONS WHICH SHOULD RESPOND WELL TO SULFONAMIDE THERAPY

Virus infections:	Gonococcus infections:
Trachoma	Conjunctivitis
Inclusion conjunctivitis*	Iridocyclitis
Lymphogranuloma venereum	Pyocyanus infections:
Hemolytic streptococcus infections:	Ulcers
Conjunctivitis†	Proteus infections:
Corneal ulcers	Conjunctivitis*
Endophthalmitis	Coliform group infections:
Orbital cellulitis	Conjunctivitis*
Impetigo*	Hemophilus influenza infections:
Staphylococcus infections:	Conjunctivitis*
Dacryocystitis	Orbital cellulitis
Conjunctivitis*	Friedländer bacillus infections:
Ulcers*	Ulcers†
Endophthalmitis	Dacryocystitis
Blepharitis*	Meningococcus infections:
Orbital cellulitis	Endophthalmitis
Impetigo*	Conjunctivitis
Pneumococcus infections:	
Dacryocystitis	
Conjunctivitis*	
Ulcers†	
Endophthalmitis	
Orbital cellulitis	

* Local therapy preferred.

† Combined oral and local therapy preferred.

(Thygeson, P., and Stone, Wm., Jr.:⁶ N. Y. State J. M.)

TABLE 3—OCULAR INFECTIONS IN WHICH PERORAL ADMINISTRATION OF SULFONAMIDES MAY BE OF VALUE AND DESERVES A TRIAL

Actinomyces bovis:	Brucella melitensis abortus suis*
Actinomycosis	Keratitis
Clostridium welchii:	Uveitis
Endophthalmitis	Choroiditis
Hemophilus ducreyi:	Erythema multiforme (cause unknown):
Soft chancre of lid or conjunctiva	Conjunctivitis
Streptococcus viridans.	Keratitis
Conjunctivitis	Moraxella lacunata (diplobacillus of Morax-Axenfeld):
Endophthalmitis	Conjunctivitis*
Klebsiella pneumonia (Friedländer):	Marginal ulcers*
Ulcers	Moraxella duplex (diplobacillus of Petit):
	Central ulcers

* Local therapy more important

(Thygeson, P. and Stone, Wm. J. Jr. N. Y. State J. M.)

two days, instead of the usual seven days. Absence from duty because of conjunctivitis has been materially reduced. The danger of spreading the infection has been lessened. Not the least important of the results of this treatment has been that the over-taxed clinical facilities of the dispensary have been relieved to some extent.

Serpent Ulcer: Since serpent ulcers are caused by pneumococcus, and rarely by other organisms, all of which are sensitive to sulfonamides, one is justified in using these drugs. Reports are available showing the value of chemotherapy in this condition.

Endophthalmitis-Panophthalmitis: As in other diseases accompanied by purulent matter and detritus, sulfonamides to be effective must be used early in these conditions. However, even in ordinary clinical cases, where the time of initial treatment frequently cannot be chosen, the results are not entirely discouraging.

Sulfonamides also appear to have beneficial effects on such conditions as *pyogenic infection of the skin of the eyelids, inclusion conjunctivitis, blepharitis, and cellulitis of the lids and orbit.*

Gradle and Harrison⁵ treated *epidemic keratoconjunctivitis* locally with a solution containing one per cent sodium sulfathiazole, stabilized by 0.8 per cent of sodium sulfite to which has been added 0.1 per cent of desoxyephedrine. The solution is said to be stable, nonirritating, and buffered to a pH of 9.0. The toxicity is low, the lethal dose for mice being approximately 100 mg. per kg. of body weight. Gradle used the solution as eye-drops, instilling two drops in each eye three to five times in 24 hours. Harrison used one drop in the affected eye every waking hour. In all cases the treatment was continued for a reasonable period of several weeks after the acute phase had subsided. It produces a milk-smarting sensation that disappears within a minute or two.

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ORTHOPEDIC SURGERY

In the use of sulfonamide therapy in orthopedic surgery, says Key,¹ it seems advisable to divide the patients into the following groups: Patients with (1) clean operative wounds; (2) contaminated traumatic wounds; (3) acute pyogenic infections; and (4) chronic pyogenic infections.

I. Clean Operative Wounds: The routine use of the sterile dry powder of one of the sulfonamide drugs in all clean operative wounds during the past two years has confirmed the value of

the procedure and has led me to believe that for orthopedic surgeons this affords the widest field of usefulness for these preparations. During this period I have used sulfanilamide in 150 cases, sulfathiazole (in sterile ampules supplied by the Abbott Laboratories) in 70, and a mixture of sulfathiazole and of sulfanilamide (supplied by Hynson, Westcott, and Dunning) in 23. In none of these has a postoperative infection occurred. This series represents a good many more wounds than patients, because many of the patients had two or more separate incisions.

Under the best of operative conditions a certain percentage of postoperative infections is unavoidable. Since this is true and since one is not able to determine beforehand which wounds will become infected, it must be admitted that every so-called clean operative wound is potentially an infected wound. If, in addition to using every precaution to prevent operative infection, one can place within the wound a sterile substance, which will prevent the growth of any casual bacteria which may have gotten into the wound through an accidental break in operative technic or from the surrounding air, and at the same time know that this substance will not seriously injure the patient or interfere with the healing of the wound, it seems reasonable to use this substance.

The experience with 243 cases demonstrates that sterile sulfanilamide and sulfathiazole are suitable substances for implantation in clean operative wounds, and that their use in this manner tends to lessen the incidence of postoperative infections. In this series there has not been any appreciable interference with the healing of the wounds. In a few of the early cases in which too much of the drug was placed in small wounds, there was a tendency to the accumulation of an excess amount of serum in the wound, and in two cases this serum was expressed after the sutures were removed. In neither instance, however, was there any evidence of infection, and the wounds healed by primary intention except for the small area left open after the expression of the serum, and here the healing was delayed for a few days. During the past year and a half there have been no such

instances, as during this time the amount of the drug used has been relatively small—rarely over 5 Gm. in one operative wound and in many instances only 1 or 2 Gm. or even less in small wounds, the object being not to place enough of the powder in the wound to interfere with the coaptation of the wound surfaces or to permit the formation of aggregates in the depth of the wound. One patient developed a bedsore which interfered with the healing of a spinal fusion wound, but this was due to poor postoperative care and not to the use of the drug.

The next question that arises is whether or not the local implantation of the drug tends to cause toxic symptoms in the patients. In certain instances there was an unexplained elevation of temperature after the operation. This occurred in seven cases of the sulfanilamide series. It has seemed to be somewhat more frequent with the use of sulfathiazole than with sulfanilamide, but the data on this series are not yet complete. In no instance did the rise of temperature last more than a few days, nor did it do any harm other than cause anxiety to the surgeon. There was no evidence of toxicity in cases in which the drug has been used locally in clean operative wounds. Three patients had a rash after the operation, but two of these were patients with chronic osteomyelitis who were also taking the drug by mouth. The third was a small child, who had a relatively large amount of sulfanilamide implanted in a tuberculous cavity in the ilium. It is thus evident that the drug can be used locally in clean operative wounds with safety.

The rationale of the procedure is that by the use of the drug in this manner a high concentration—that is, a saturated solution—of the drug is brought into direct contact with any organisms which may be present in the wound. This concentration of the drug in the wound lasts approximately 48 hours—that is, until the drug is absorbed and excreted. It is probable that the sulfathiazole lasts longer. The time during which the drug remains in the wound will vary directly with the amount implanted and indirectly with the blood supply of the area and with the surface exposed for absorption. In tissues well supplied with

blood the absorption is more rapid than it is in areas where the blood supply is scanty. It can be placed in joints and other body cavities and apparently does no harm to the lining of these cavities. However, it is to be noted that in large cavities, such as the peritoneum or the pleura, an extensive surface is exposed to the drug, and consequently the absorption may be unusually rapid and cause high concentrations of the drug in the blood. For this reason it seems advisable to use a mixture of sulfanilamide and the less soluble sulfathiazole in these cavities.

In addition to placing the powder in the wound before it is sutured, a small amount is sprinkled along the suture line after the skin is closed. The dressing is then put on and the drug will tend to saturate the blood or serum which drains from the wound and thus prevent the development of stitch abscesses. This is especially true if the wound is encased in a plaster of Paris cast in which it is undesirable to change the dressing for some time.

It is to be emphasized that the use of the drug in the wound for the prevention of infection does not warrant any letting down in surgical technic, because it is not infallible, and I know of four instances in which postoperative infections have occurred after sulfanilamide powder has been placed in so-called clean wounds.

2. Contaminated Traumatic Wounds: These are lacerations or compound fractures, which are treated before sufficient time has elapsed after the injury to permit the development of an actual infection in the tissues. In civilian life it is usually stated that a wound is not considered infected until from 6 to 12 hours after the injury, the time varying inversely with the amount of damage to the tissues; that is, in a wound with relatively little damage to the tissues a greater amount of time will elapse before actual infection develops, other things being equal.

There is considerable difference of opinion as to whether or not such wounds should be sutured. It has been my custom to close such wounds by primary suture after a careful débridement and expect primary healing. If I was not satisfied that I had done an adequate débridement and removed all devitalized

tissue and foreign matter in the wound, it was packed open with petrolatum gauze. This method has been used for the last 20 years and most such wounds have been sutured immediately with satisfactory results. By the use of sulfanilamide or sulfathiazole powder in the wound, or a mixture of the two, a wound can be sutured with more assurance than could the same wound without the use of the powder. In other words, the powder will tend to keep down the infection until the clearing mechanism of the body has had a chance to eliminate the bacteria. That most compound fractures in civilian life can be débrided and sutured primarily with satisfactory results if sulfanilamide powder is implanted in the wound is amply proved by the series of such cases reported by Jensen, Johnsrud, and Nelson, and by Jackson.

If one believes that these wounds should not be sutured after débridement, but should be left open and the wound packed with petrolatum gauze or with other material, in order to permit drainage, then the probably mild infection which will eventually develop on the surface of the wound will be minimized by sprinkling the powder over the surface of the wound before the petrolatum gauze or other packing material is inserted.

The use of sulfanilamide or sulfathiazole in the wound does not permit the letting down of any of the standards for a complete débridement of the wound, nor does it eliminate the necessity for adequate reduction of the fracture and immobilization of the part after the wound has been sutured or after the wound has been packed open. It does, however, permit the use of internal fixation in the treatment of compound fractures.

In military surgery, which is occupying such a prominent place in our thoughts, the use of sulfanilamide or sulfathiazole powder, or a mixture of the two, will lessen the incidence of infection after wounds have been débrided. However, contaminated war wounds should not be sutured, and especially is this true in a war of movement, where the men are treated in casualty clearing stations or other hospitals, and are then moved on after a few hours or after a longer interval.

When a surgeon débrides and sutures a contaminated wound he should assume the obligation of watching this patient until the danger of infection has passed. For this reason it is not wise to advocate débridement and immediate closure of war wounds in military surgery. Many of these will have to be left open, not because they could not have been sutured under favorable conditions, but because it is not possible to keep the patients in the hospital and under the care of the operating surgeon until sufficient time has elapsed so that the danger of infection is no longer present. It is further to be noted that the transportation of such patients, either in casts or in splints, causes a variable amount of movement of the part and exposure of the patient and is accompanied by some pain. Movement of the part lowers the local resistance, and pain and exposure lower the general resistance. Consequently, transportation of a recently operated compound fracture tends to favor the development of an infection in the wound.

In civilian life the movement of the part, pain, and exposure can be reduced to a minimum, but under war conditions, and especially those of total war, military necessity may cause the wounded who have recently been operated on to be transported when and if the opportunity presents itself and by whatever means are available. Consequently, wounds in war should be débrided, sprinkled liberally with sulfanilamide or sulfathiazole or, preferably, a mixture of the two, packed open with petrolatum or plain gauze, and immobilized in a cast or splint, which will maintain the reduction effected during the operation.

The question immediately arises as to whether or not these men should also be given sulfanilamide or sulfathiazole by mouth. Ordinarily in civilian practice I do not give sulfanilamide or sulfathiazole by mouth to a patient with a recently débrided and sutured contaminated wound. It is believed that adequate débridement plus local implantation of the drug are sufficient and this has been my experience in the past. On the other hand, in certain cases in which a little more time than is considered safe has elapsed or I am not quite sure of the efficiency of the

débridement, in addition to placing the drug in the wound, I give the patient full doses of sulfathiazole by mouth before the operation, and as soon as he is able to take it after the operation (usually 2 Gm. is given before the operation and 1 Gm. every four hours for the first two days after the operation). If there is no evidence of infection at the end of two days the drug is stopped entirely, or it may be tapered off. Fluids are forced while sulfathiazole is being given in order to prevent damage to the kidneys. This plan seems suitable for war wounds, in which the danger of infection is greater than in civil life.

3. **Acute Pyogenic Infection:** These patients fall into two groups: (1) Those with contaminated wounds in which sufficient time has elapsed to permit the development of infection; and (2) acute hematogenous pyogenic infections, such as acute osteomyelitis and acute arthritis.

In the first group the wound, usually a compound fracture, is open and is draining but the drainage is inadequate. There is usually a mixed infection, and the bacteria are not all on the surface of the wound but have grown into the tissues, and the organisms of gas gangrene may be present. These patients are ill with a systemic infection and need the drug which will most effectively combat a mixed infection. This is sulfathiazole, and it should be given by mouth in full doses or, if necessary, as the sodium salt intramuscularly in strong solutions or intravenously in dilute solutions. .

In addition to the general administration of the drug, the wound should be adequately drained, foreign bodies should be removed, and obviously devitalized tissue should be excised. All acutely infected wounds should be left wide open. In gas gangrene, involved muscle should be excised and the patient should be given large doses of the polyvalent serum.

After the operation is completed and the toilet of the wound is made, the surface of the wound and its depths should be sprinkled liberally with sulfathiazole or with a mixture of sulfathiazole and sulfanilamide, the amount of the drug being considerably more than is used in wounds which are being closed.

This is for two reasons. The first is that absorption of the drug will be less and the second is that with an established infection it is probable that large numbers of bacteria will remain in the tissues even after an adequate débridement.

Finally, the wound should be immobilized and the patient should receive supportive treatment, including a transfusion of blood or plasma if indicated, and the sulfathiazole should be continued by mouth until evidence of general infection has subsided.

In hematogenous pyogenic osteomyelitis or pyogenic arthritis the problem is somewhat similar, except that the focus of the infection has not been drained. At the present time there is considerable difference of opinion as to whether or not this local focus should be attacked surgically. Many believe that acute hematogenous osteomyelitis is a general disease or septicemia, of which the local focus in the bone is but one manifestation, and that the patient should be treated medically rather than surgically. I do not concur in this belief. It is my opinion that the local infection in the bone should be drained as soon as it is safe to do so; that is, as soon as the patient is in condition to stand the operation.

The chemotherapeutic agents at our command cannot be relied on to sterilize an abscess cavity in the bone when they are administered by mouth. It is true that when sulfanilamide or sulfathiazole is given by mouth a concentration is eventually obtained in the fluid of the abscess cavity which approaches that present in the blood. In my experience the concentration obtained in the pus has been approximately 50 per cent of that present in the blood. However, this concentration is not sufficient to kill staphylococci.

There is no doubt that in certain cases of acute pyogenic osteomyelitis, if large doses of sulfathiazole are given, the disease in the bone will subside and the bone will eventually heal. How frequent these cases are, I do not know. I have seen one. On the other hand, I have seen patients who developed metastatic foci while they were receiving full doses of sulfathiazole, and

who eventually became osteomyelitic derelicts as a result of widespread destruction of bones and joints. Other patients have died without operation. I have also seen patients with mild pyogenic infections in bone get well without surgical intervention or chemotherapy.

Sulfathiazole rather than sulfanilamide should be used in every case of acute pyogenic osteomyelitis. It should be given in full doses by mouth if possible or intramuscularly or intravenously if necessary. As soon as the patient is in condition for the operation, the focus in the bone should be drained. No attempt should be made to remove the entire area of the disease. At the operation sulfathiazole powder or a mixture of sulfanilamide and sulfathiazole should be implanted in the wound in liberal amounts. The wound should be packed loosely with petrolatum gauze and the extremity immobilized in a plaster cast. Supportive treatment of the patient should be continued and the patient should be given full doses of sulfathiazole by mouth until his temperature has subsided. At the same time fluids should be forced. For a very toxic patient the staphylococcus antitoxin should be used if it is available. The drug will exert a favorable influence on the septicemia, lower the mortality, tend to decrease the amount of destruction of bone, and decrease the number of metastatic foci which tend to develop in this disease.

The same is true of acute pyogenic arthritis. The joint should be opened, washed out with physiologic solution of sodium chloride, a liberal amount of sulfathiazole powder should be implanted in the joint cavity, and, as a rule, the joint should be left open. In certain relatively mild infections I have closed the joint and immobilized it, and the wounds have stayed healed and a useful joint has resulted.

4. Chronic Pyogenic Infections: These include chronic osteomyelitis and chronic infections of soft tissues, either deep infections or surface infections. As staphylococci are usually present, sulfathiazole is the drug of choice, although sulfanilamide powder in concentrated form will tend to lessen the amount of drainage

and decrease the activity of the infection in the wound. Either drug is useful as a dusting powder for chronic surface infections and tends to lessen the amount of secretion in chronic osteomyelitis. But they cannot be expected to cure chronic infection in the bone. The same fact is true of sulfathiazole by mouth in chronic osteomyelitis. In certain instances in which the condition is nonoperable, as in extensive involvement of the shaft of the femur, I have given patients the drug by mouth over a considerable period, and they have felt better and the discharge from the wound has been less. None of these infections, in my experience, has healed and remained healed. The chief use of the drug in chronic osteomyelitis is that recently pointed out by Dickson and Diveley. They have shown that chronic osteomyelitis can be treated surgically and the wound can then be sprinkled with sulfathiazole powder and closed.

I have followed this procedure in 17 cases and in none of these have there been any untoward results. Fourteen healed by primary intention. In the three others there was a definite reason for the failure of primary healing. One of these was an extensive disease of the tibia in which, after sequestrectomy and saucerization, it was not possible to close the wound completely. It eventually healed by granulation. Another tibia was operated on eight weeks after the acute focus in the bone had been drained. This was cleaned out thoroughly and the wound was almost closed. This wound is now healed. In the third case, in which operation was performed four weeks after the onset, a large abscess was drained, the femur was opened, and extensive necrosis was present in the lower end of the shaft. The drug was given by mouth as well as locally and the wound was packed open. There had been extensive destruction of bone and this child may require a second operation for the removal of a sequestrum.

The operation is most successful in chronic osteomyelitis, in which sinuses can be excised, all dead bone can be removed, and the walls of the wound can be closed. For one or two days before the operation the patient is given full doses of sulfathiazole by mouth—that is, 1 Gm. every four or six hours—and this is con-

tinued after the operation until danger of a flare-up of the infection is past, usually only for three or four days. The dose is then gradually tapered off.

In operating in such cases I have not used any deep sutures, but have closed only the skin and fascia with large through-and-through sutures of silkworm gut. After the operation the limb is immobilized in a plaster of Paris cast without drainage. When the drug is being given by mouth toxic manifestations are more apt to occur, and in two of the 17 cases a rash developed after the operation.

REFERENCE

1. Key, J. A.: J. A. M. A. 117:409 (Aug. 9) 1941.



OSTEOMYELITIS

See page 137



OTITIS MEDIA

See page 142



OTOLARYNGOLOGY

The dosage of sulfonamides is greater and continued over a much longer period, according to Porter,¹ in otolaryngology than in general medicine or pediatrics. The author has found sulfadiazine the most effective and least toxic of the sulfonamides. It has the greatest degree of penetration into the cerebrospinal fluid and thus is very important in the treatment of meningitis of otitic or sinus origin. Sulfathiazole has the least degree of penetration and is the most dangerous of the sulfonamides for otolaryngological use.

Chemotherapy does not supplant surgery; rather, it is an extremely valuable adjunct. Because the sulfonamides can affect inaccessible areas, such as enclosed pus, bone necrosis, and infected thrombi (whether in the mastoid, frontal bone, or cal-

varium) only through the blood stream, it is obvious that such pathology must first be removed completely by surgery. This was proved repeatedly by the author's results in treating osteomyelitis of the frontal bone and lateral sinus thrombosis.

Treatment with a combination of sulfonamides and heparin has been responsible for the spectacular recovery of many cases of cavernous sinus thrombosis. The heparin will not dissolve an already formed clot, but will prevent further clot formation, thereby permitting the drug to penetrate the infected wall of the vein.

Acute sinus conditions respond beautifully to sulfonamide therapy. In the author's private practice, 28 of 30 patients were cured completely, and two required minor surgical interference to promote sinus drainage.

For most effective use sulfonamides must be administered during the early stages of a disease and in conjunction with immune sera when available. In all cases the author prefers to delay surgery until an optimum blood level has been established.

Bowers² believes that sulfonamide therapy is efficient and safe in sinusitis. I, personally, have not seen, in the treatment of sinusitis, he says, any flare-ups following the discontinuance of the drug, such as frequently occur in mastoiditis. Recently Shambaugh reported two patients with sinusitis on whom chemotherapy was used, who apparently recovered, yet later developed meningitis and died. To my mind, this report constitutes a warning rather than a contraindication to the use of the drug. I have also tried chemotherapy on cases of chronic sinus disease, with thick pus in the antral washings and thickened membrane in the sinuses; in these patients I have had very negative results. Apparently the drug works best, in sinusitis, in the presence of a fulminant infection. According to Shambaugh's report, it may have a masking effect, just as in mastoiditis, and will therefore need careful watching even after the patient is clinically well. The best method of checking on this masking effect is by means of x-rays. I have seen patients, clinically recovered from frontal sinus infection, whose x-rays showed prog-

ress in bone destruction. It is safer, in the presence of an undrained focus of infection, not to rely too much on chemotherapy alone.

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2. BOWERS, W. C.: *Eye, Ear, Nose, and Throat Monthly* 22:293 (Aug) 1943.



PANOPHTHALMITIS

See page 266



PEMPHIGUS

See page 168



STREPTOCOCCIC PERICARDITIS

The therapeutic efficiency of sulfanilamide and an acetylated derivative of 4,4'-diaminodiphenylsulfone hydrochloride in experimental beta hemolytic streptococcus pericarditis in rabbits was compared by Lebowich.¹ After trials of many substances, 1 molar acetic acid was selected as the most satisfactory agent for reducing the acute toxicity of the latter drug. The acetic acid administered with the sulfone compound definitely lessened the severe acute and chronic toxic effects of the sulfone compound in rabbits without materially affecting the curative value of the drug. The acetylation of the sulfone hydrochloride served as a detoxicating mechanism. There was considerable variation in the acetylation of the drug, even in the presence of added 1 molar acetic acid in different infected animals. The acetylated derivative of 4,4'-diaminodiphenylsulfone hydrochloride had a distinctly beneficial effect on the natural course of experimental beta hemolytic streptococcus pericarditis in rabbits. It considerably increased the number of cured survivors, in comparison with

their complete absence in the sulfanilamide-treated group, and definitely prolonged the average duration of life beyond that of control and sulfanilamide-treated animals. The most effective results were among 50 rabbits in which treatment was initiated 12 hours after pericarditis was produced; 49 of these animals were cured. The acetylated derivative of 4,4'-diaminodiphenyl-sulfone hydrochloride was far superior to sulfanilamide in the rabbits in its effect on the infection.

REFERENCE

1. LEBOWICH, R. J.: Arch. Path. 35:253 (Feb.) 1913.



PERITONITIS

See Appendicitis and Peritonitis, page 97



PLACENTA ACCRETA

A case is reported by Smith and Seibert¹ of placenta accreta where laparotomy was absolutely contraindicated because of severe shock and sepsis. Vaginal discharge was profuse and foul smelling. Conservative treatment seemed the only alternative. Wangenstein duodenal suction was used to relieve the distention. A transfusion of 500 cc. of citrated blood was given every other day from the third to the eleventh day postpartum. On the alternate days 4 Gm. of sodium sulfapyridine were administered intravenously in 1000 cc. of isotonic solution of sodium chloride every eight hours. Five cc. of azosulfamide solution were injected intramuscularly every four hours for two days and then 2 cc. every four hours.

Under this conservative management the patient improved to the point where there ceased to be an indication for surgical intervention when her general condition would have warranted it. The placenta evidently sloughed out in the profuse, foul discharge, although no portion of it was ever recovered. Normal menstruation began in three months, which supports this assumption.

This report does not constitute an endorsement for the conservative treatment of placenta accreta which normally should be treated by hysterectomy. However, it does show that the condition of a patient with this abnormality is not necessarily hopeless, even when laparotomy is contraindicated.

REFERENCE

I. SMITH, R. I., AND SEIBERT, C. W.: J. A. M. A. 120:1417 (Aug. 22) 1942.



PLAGUE

Wagle *et al.*¹ studied 294 cases of plague in India over a four-month period. The patients received various forms of treatment in rotation as they were admitted, *i. e.*, the first received anti-plague serum, the second the usual hospital treatment of iodine solution intravenously, the third sulfapyridine, the fourth anti-plague serum, and so on. After admission 207 sulfapyridine was replaced by sulfathiazole. From admission 246 each alternate admission received sulfathiazole and the remaining cases served as controls. Nineteen cases proved not to be plague, and exclusions from the study because the patients were moribund or for some other reason, brought the total number of cases of bubonic plague in the study down to 237, which are accounted for in tables I and 2.

Sulfapyridine was given in a dosage of 1 Gm. on admission and 0.5 Gm. every four hours thereafter for seven days. Sulfathiazole was given in the same dosage. The drug was stopped if the temperature came to normal and there was a distinct improvement in the general condition. The sodium salt of the sulfonamide was given intravenously in those patients who could not take it for any reason by mouth, but these were not many.

Anti-plague serum was given in a dosage of 40 cc. on the day of admission; 20 cc. were given immediately intravenously on admission, and 20 cc. subcutaneously six hours later. The same quantity was given in the same way on the following day. Subsequent administration depended upon the severity of the case.

The iodine solution was the usual hospital treatment for plague in India. While it is believed to have curative value, the cases receiving it were considered to be controls for the other two forms of treatment. The stock solution used contained 5.5 Gm. of iodine and 8.5 Gm. of potassium iodide in 100 cc. of distilled water. This was given intravenously once daily in a dosage of 0.5 cc. diluted with 100 cc. of distilled water.

TABLE 1—ALL CASES OF BUBONIC PLAGUE TREATED

<i>Treatment</i>	<i>Number of Cases</i>	<i>Number of Deaths</i>	<i>Case Mortality Per cent</i>
Antiplague serum	70	20	28.5
Sulfapyridine	53	13	24.5
Sulfathiazole	32	5	15.6
Controls—treated with iodine solution intravenously	82	43	52.4
Totals	237	81	

TABLE 2—CASES WITH PLAGUE SEPTICEMIA AT THE COMMENCEMENT OF TREATMENT

<i>Treatment</i>	<i>Number of Cases</i>	<i>Number of Deaths</i>	<i>Case Mortality Per cent</i>
Antiplague serum	33	20	60.6
Sulfapyridine	30	13	43.3
Sulfathiazole	12	5	41.8
Controls—treated with iodine solution intravenously	40	38	95.0
Totals	115	76	

The authors regard treatment with the sulfonamides and with antiplague serum as a distinctly forward step in the therapeutics of plague. The small difference in the figures they consider due to the unequal number of cases treated. However, there is much greater ease in the administration of sulfonamides over serum. It is in the septicemic cases, the authors point out, that the sulfonamides demonstrate their superiority.

They state: "The curative value of these chemotherapeutic agents under very severe conditions is however seen in table 2, which records results obtained in septicemic cases. Plague septi-cemia is a very serious condition indeed, as the control cases, of which nearly 95 per cent died, show. In septicemic cases treated with sulfapyridine and sulfathiazole, however, the case mortality was reduced to about 40 per cent, *i. e.*, more than half of the cases treated recovered. Similar but slightly inferior results were obtained with the antiplague serum."

REFERENCE

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PNEUMONIA

In no phase of Medicine has chemotherapy been more epoch-making than in the treatment with the sulfonamide drugs of that still-to-be-dreaded killer, pneumococcic pneumonia. Flippin, Schwartz, and Domm¹ report on 1635 cases of pneumococcic pneumonia treated with sulfapyridine, sulfathiazole, or sulfadiazine. Their report follows:

Comparative Therapeutic Effectiveness

The effectiveness of a chemotherapeutic agent for the treatment of pneumococcic pneumonia may be evaluated from the study of: (1) The effect of the agent on mortality, on incidence of complications, and on the course of the disease; (2) the toxic effects on the patient, and (3) the pharmacologic behavior of the drug in man.

Mortality Rates, Incidence of Complications, and Influence of Treatment on the Course of the Disease

Sulfapyridine, sulfathiazole, and sulfadiazine were comparable in effectiveness as judged by the mortality rates (Table 1) of 9.7, 12.1, and 10.3 per cent for the three therapeutic groups. Positive blood cultures for pneumococci were obtained in 10.9, 15.0, and 22.2 per cent of patients receiving sulfapyridine, sulfathiazole, and sulfadiazine, with mortality rates of 32.5, 43.3, and 25.5 per cent respectively. However, as mentioned before,

one cannot be certain as to the significance of bacteremia as an index of the relative severity of the cases in each therapeutic group. The incidence of complications was low and comparable in the three drug-treated groups (Table 2). The most striking clinical observation with the three drugs was the frequency with which the initiation of drug therapy was followed within 24 to 48 hours by a critical drop in temperature. The action of sulfapyridine and sulfadiazine in lowering the temperature was more rapid than that of sulfathiazole, although the average duration of treatment and the average stay in the hospital was practically the same for all three drug-treated groups.

Toxic Effects

In our experience (Table 3) with these drugs in pneumococcic pneumonia, the incidence and severity of toxic reactions following sulfadiazine therapy were less than those observed in patients receiving sulfapyridine or sulfathiazole. This difference in toxicity was principally the relatively lower incidence of untoward gastrointestinal and renal manifestations associated with sulfadiazine treatment.

Pharmacologic Behavior in Man

Sulfadiazine, given orally, yields higher concentrations of the free drug in the blood and smaller proportions of acetylated drug in the blood and urine than do sulfapyridine or sulfathiazole. Furthermore, acetylsulfadiazine is more soluble in urine than is acetylsulfapyridine or acetylsulfathiazole. These differences in the relative degree of acetylation and solubility of the acetyl derivatives appear to have an influence on the incidence and severity of urinary tract complications following the use of these drugs (Table 3). When these compounds are administered intravenously, higher concentrations of the drug are maintained for longer periods with sodium sulfadiazine than with sodium sulfapyridine or sodium sulfathiazole. This is of decided value in the control of infection in certain types of cases.

On the basis of the foregoing data it would appear that the drug of choice for the treatment of pneumococcic pneumonia at the present time is sulfadiazine.

Routine Management of Pneumococcic Pneumonia

Early Treatment: With the exception of the age of the patient (Chart 2) and certain other factors beyond the physician's control, the length of time that elapses between the onset of the infection and the beginning of specific treatment is the most

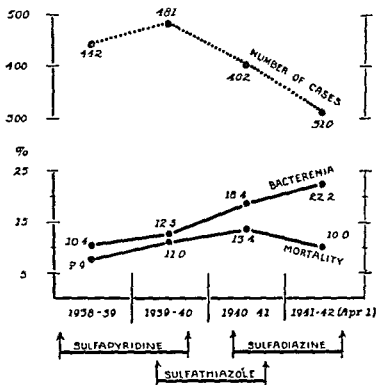


Chart 1—Number of cases treated, incidence of bacteremia, and mortality percentage in each year of this study. The three drugs were employed for the most part over the designated periods. (Flippin, H. P., et al.: *J. A. M. A.*)

important single controllable factor in the prognosis of pneumococcic pneumonia. As indicated in Chart 3, there was a definite increase both in the mortality rate and in the incidence of complications in those cases in which chemotherapy was started after the first 48 hours of the illness. Hence the best results with these drugs are obtained when they are administered early in the infection, while the number of bacteria is still limited and the

TABLE 1.—DISTRIBUTION OF TYPES, BACTEREMIA, AND MORTALITY RATES

Type	Self-pyridine Treated						Sulfathiazole Treated						Sulfadiazine Treated						All Cases						Totals					
	All Cases			Bacteremic Cases (10.9%)			All Cases			Bacteremic Cases (13.0%)			All Cases			Bacteremic Cases (22.4%)			All Cases			Deaths			All Cases			Deaths		
	No	Deaths	%	No	Deaths	%	No	Deaths	%	No	Deaths	%	No	Deaths	%	No	Deaths	%	No	Deaths	%	No	Deaths	%	No	Deaths	%	No	Deaths	%
1	174	8	4.6	1	1	100	81	4	4.9	3	1	33.3	103	7	6.8	32	4	12.5	338	19	5.6	1	0	0	1635	173	10.6%	249	81	32.5%
2	52	24	46.2	1	1	100	14	17	121.4	1	1	100	19	0	0	5	0	0	85	5	5.9	3	0	0	1635	173	10.6%	249	81	32.5%
3	224	5	2.2	1	1	100	16	6	37.5	1	1	100	58	11	19.0	11	0	0	258	52	20.1	6	0	0	1635	173	10.6%	249	81	32.5%
4	44	6	13.6	1	1	100	32	0	0	6	0	0	34	4	11.8	7	0	0	110	15	13.6	15	0	0	1635	173	10.6%	249	81	32.5%
5	20	21	105.0	1	1	100	24	0	0	0	0	0	30	1	3.3	9	0	0	15	3	20.0	15	0	0	1635	173	10.6%	249	81	32.5%
6	21	2	9.5	1	1	100	14	4	28.6	0	0	0	11	4	36.4	1	0	0	46	9	19.6	10	0	0	1635	173	10.6%	249	81	32.5%
7	48	4	8.3	1	1	100	11	2	18.2	1	1	100	44	4	9.1	8	0	0	131	9	6.9	10	0	0	1635	173	10.6%	249	81	32.5%
8	50	7	14.0	1	1	100	33	5	15.2	1	1	100	41	4	9.8	9	0	0	121	9	7.4	10	0	0	1635	173	10.6%	249	81	32.5%
9	6	1	16.7	1	1	100	8	7	87.5	1	1	100	9	0	0	2	0	0	23	1	4.3	5	0	0	1635	173	10.6%	249	81	32.5%
10	8	2	25.0	1	1	100	0	0	0	0	0	0	2	0	0	0	0	0	17	1	5.9	1	0	0	1635	173	10.6%	249	81	32.5%
11	10	0	0	1	1	100	0	0	0	0	0	0	10	0	0	1	0	0	16	1	6.3	1	0	0	1635	173	10.6%	249	81	32.5%
12	2	0	0	1	1	100	0	0	0	0	0	0	8	0	0	0	0	0	26	1	3.8	1	0	0	1635	173	10.6%	249	81	32.5%
13	14	1	7.1	1	1	100	4	4	100	0	0	0	4	0	0	0	0	0	14	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
14	27	9	33.3	1	1	100	20	4	20.0	0	0	0	13	2	15.4	4	0	0	15	2	13.3	3	0	0	1635	173	10.6%	249	81	32.5%
15	8	3	37.5	1	1	100	4	7	175.0	0	0	0	15	0	0	1	0	0	20	3	15.0	3	0	0	1635	173	10.6%	249	81	32.5%
16	5	3	60.0	1	1	100	0	0	0	0	0	0	2	0	0	0	0	0	15	3	20.0	4	0	0	1635	173	10.6%	249	81	32.5%
17	3	0	0	1	1	100	0	0	0	0	0	0	2	0	0	0	0	0	15	3	20.0	4	0	0	1635	173	10.6%	249	81	32.5%
18	16	1	6.3	1	1	100	10	8	80.0	0	0	0	12	0	0	0	0	0	31	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
19	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	35	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
20	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
21	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
22	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
23	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
24	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
25	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
26	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
27	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
28	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
29	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
30	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
31	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
32	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
33	12	1	8.3	1	1	100	0	0	0	0	0	0	12	0	0	0	0	0	21	0	0	6	0	0	1635	173	10.6%	249	81	32.5%
Totals	733	72	9.7%	80	26	32.5%	447	54	12.1%	67	29	43.3%	455	47	10.3%	102	26	25.5%	1635	173	10.6%	249	81	32.5%	106%	10.6%	23.5%	10.6%	23.5%	10.6%
Mortality	9.7%	32.5%	12.1%	43.3%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%
Gross mortality . .	9.7%	32.5%	12.1%	43.3%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%	10.3%	25.5%

(Flüggen, H. P., et al.: J. A. M. A.)

extent of tissue involvement is at a minimum. Certainly, sulfadiazine treatment should not be withheld just because the case is considered mild. Likewise, the use of drug should not be delayed in a suspected case of pneumonia until signs of consolidation have appeared. Obviously, this does not mean that every person suffering with a mild infection of the upper respiratory tract is to be regarded as a pneumonia suspect.

Adequate Chemotherapy: Theoretically, in order to obtain maximum therapeutic results with sulfadiazine in pneumococcic pneumonia, it is necessary to administer the drug in such a manner as to obtain an effective concentration of free drug in the blood as soon as possible, and to maintain an adequate level until the patient has developed sufficient immunity against the infection to prevent a relapse. However, we have been unable to establish an optimal blood concentration for sulfadiazine in the treatment of pneumococcic pneumonia, and, furthermore, methods for determining the immunity response of patients receiving sulfadiazine are still in the experimental stage and are as yet of doubtful clinical significance. Thus it is difficult to outline a course of sulfadiazine therapy which will theoretically be effective, but it seems reasonable, for practical purposes, to administer the drug in a manner which experience indicates will probably be adequate for the treatment of pneumococcic pneumonia of adults.

In general, the oral route has proved to be the most practical method of administering sulfadiazine, although in certain instances in parenteral use is indicated. (*See pages 26 and 44.*) As a rule, sulfadiazine is readily absorbed from the intestinal tract into the blood stream, reaching levels of 4 to 6 mg. of free drug per 100 cc. within four to six hours after the oral administration of a single (3 to 4 Gm.) dose. After the fourth to the sixth hour the amount of drug in the blood begins to diminish and, if the blood concentration of the drug is to be maintained or increased, it is necessary to administer additional drug in smaller amounts every four to six hours until the total dosage has been given. Since varying blood levels of the drug result in diminished thera-

peutic effectiveness, it is important to adhere to this schedule of dosage. As already mentioned, we have been unable to determine any definite correlation between the effectiveness of sulfadiazine and the concentration of free drug in the blood, although it appears that, if a free blood level of 5 to 10 mg. per 100 cc. is maintained, satisfactory results may be expected. In this connection it should be remembered that such factors as drug absorption and kidney function tend to influence the amount of drug found in the blood, since the drug concentration reached in the blood is dependent both on the rate of entry into, and the rate of exit from, the blood stream. On the basis of these considerations, and after employing several schemes of dosage, we have adopted the following dose schedule for the treatment of pneumococcic pneumonia of adults with sulfadiazine:

An initial 3 Gm. dose of sulfadiazine is given orally and followed by 1 Gm. every six hours thereafter, until the temperature has remained normal for 48 hours and the patient shows clinical evidence of improvement. It is possible in most cases to adhere to this six-hour-dose schedule, but occasionally, when a higher

TABLE 2—COMPLICATIONS

Complication	TREATMENT			Total 1,635 Cases	
	Sulfa- pyridine 733 Cases	Sulfa- thiazole 447 Cases	Sulfa- diazine 455 Cases		
	Incidence, per cent	Incidence, per cent	Incidence, per cent	Incidence, per cent	Mortality, per cent
Massive pleural effusion	2.2	2.7	2.4	2.3	2.6
Empyema . .	1.9	1.8	2.2	2.0	28.1
Endocarditis	0.5	0.7	1.8	0.7	100.0
Lung abscess	0.3	0.7	0.7	0.5	75.0
Metastatic abscess	.	0.4	0.2	0.2	66.6
Meningitis .	0.1	0.2	0.2	0.2	100.0
Otitis media .	0.1	0.4	.	0.2	
Phlebitis.	0.1	..	0.2	0.1	
Pericarditis .	..	0.2	0.2	0.1	100.0

(Flippin, H. F., et al.: J. A. M. A.)

blood level of drug is desired, the 1-Gm. dose is given at four-hour intervals until the desired drug concentration in the blood is obtained. In order to give sulfadiazine parenterally it is necessary to employ its sodium salt. Best results with sodium sulfadiazine parenterally are obtained with its intravenous use. For intravenous therapy a five per cent solution of sodium sulfadiazine in sterile distilled water is employed. Obviously, when the drug is administered by vein, higher blood levels of free sulfadiazine (10 to 18 mg. per 100 cc.) are obtained more rapidly (within 15 minutes) than when equal amounts (3 to 4 Gm.) are given by mouth. As a rule, this form of therapy is resorted to for those patients in whom a more rapid elevation of the blood level of drug is desired or when oral medication is impracticable. Patients who are unable to take sulfadiazine by mouth are given an initial 3 to 4 Gm. dose of sodium sulfadiazine intravenously, followed by 2 Gm. every 12 hours thereafter until the total dose

TABLE 3—TOXIC REACTIONS

Toxic Reaction	TREATMENT		
	Sulfapyridine 733 Cases	Sulfathiazole 447 Cases	Sulfadiazine 455 Cases
	Incidence, per cent	Incidence, per cent	Incidence, per cent
Vomiting	52.2	19.7	3.1
Hematuria: Microscopic	10.1	9.6	4.4
Gross	1.2	0.9	0.2
Loin pain	0.5	0.4	
Renal calculi	0.4	0.4	
Anuria	0.1		
Dermatitis	1.9	3.8	1.1
Conjunctivitis		0.9	
Episcleritis			0.2
Acute hemolytic anemia	0.1		
Leukopenia	3.0	2.5	2.0
Neutropenia	0.8	0.7	
Fever?	5.0	5.4	2.2
Psychosis?	4.8	3.1	5.5

(Flaggio, H. F., et al.: J. A. M. A.)

has been given. Frequently it is well to give seriously ill patients a large initial dose of drug (3 to 4 Gm.) by vein and at the same time start giving 1-Gm. doses every four to six hours by mouth. In general, the total dosage of sulfadiazine is 20 to 30 Gm.,

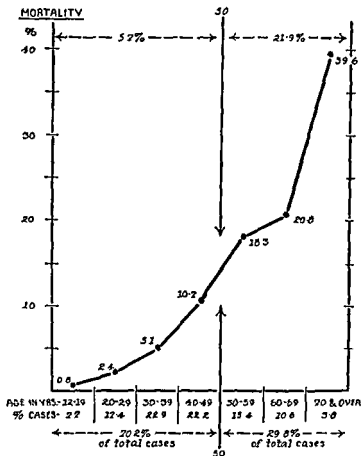


Chart 2—Influence of age on mortality in 1635 cases,
(Flippin, H. F., et al : *J. A. M. A.*)

depending on such factors as the day of disease when treatment was started, the presence of bacteremia, spread of the infection, complicating diseases, kidney function, and drug toxicity. It is to be remembered that, once drug treatment has been started, it

is to be continued, unless signs of severe toxicity develop, until convalescence is established. Not infrequently a fall in temperature proves deceptive and a spread or recurrence in the infection occurs if chemotherapy is stopped too early. Although it is not generally necessary, a safe procedure to follow, when in doubt, is to reduce the dose of drug gradually over a period of days and watch the patient carefully for evidence of recurrent infection.

Fluid Balance: Sulfadiazine, regardless of its route of administration, is excreted mostly in the urine, and its elimination is reduced in the presence of kidney damage. Therefore, with a decrease in kidney function an increase in drug concentration in the blood occurs and, should the volume of urine become low, the possibility of stone formation in the urinary tract by precipitation of crystals of acetylsulfadiazine is greatly increased. However, the excretion of sulfadiazine, both the free and acetylated forms, is definitely increased by an increased rate of flow of urine. Hence it is of importance, in order to facilitate the excretion of the drug by the kidneys, to maintain a urinary output of at least 1200 cc. in each 24-hour period. This is best obtained by forcing fluids, either by mouth or, if necessary, parenterally.

Use of Alkalis: The renal complications following sulfadiazine therapy are due in part, if not entirely, to the presence in the urinary tract of crystals composed of the drug, especially the acetyl portion. Since crystalluria from sulfadiazine appears to be less frequent in an alkaline urine, it is advisable to administer alkalis to patients receiving the drug. It has been our practice to give equal amounts of sodium bicarbonate or sodium citrate to all sulfadiazine-treated pneumonia patients who showed evidence of renal impairment, and it seems practical to administer an alkali routinely to all patients receiving sulfadiazine therapy.

Supportive Measures: Regardless of the therapeutic value of sulfadiazine in pneumococcic pneumonia, it is not to be used to the exclusion or neglect of established supportive measures.

The pneumonia patient requires competent nursing care, complete mental and physical rest, sufficient fresh air, easily digested food, and adequate bowel elimination. The intelligent use of morphine still constitutes one of our principal aids in the control of certain disturbing features of this disease, such as apprehen-

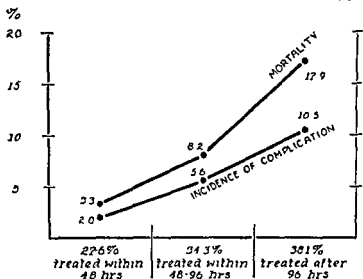


Chart 3—Mortality and incidence of complications in relation to the length of time that elapsed between the onset of the disease and the beginning of treatment in 1635 cases. (Flippin, H. F., et al.: *J. A. M. A.*)

sion, restlessness, and pain. Fortunately, the severity of abdominal distention is less pronounced in pneumonia patients receiving chemotherapy than was formerly observed, although occasional patients will require enemas, rectal tubes, local heat to the abdomen, and the use of drugs like solution of posterior pituitary. In general, it is best to avoid the employment of cathartics. Digitalis should be administered when indicated, but not as a routine procedure. We know of no medication or food which cannot be given to pneumonia patients treated with sulfadiazine.

Control of Drug Toxicity: Although the incidence and severity of toxic reactions following the use of sulfadiazine in pneumococcal pneumonia are not as severe as those encountered

with sulfapyridine or sulfathiazole therapy, it must be remembered that the drug is not entirely harmless to the host.

The vomiting that sometimes follows treatment with sulfadiazine is rarely so severe as to necessitate stopping the drug, but if it becomes so it is advisable to check the fluid and salt balance. Cutaneous and episcleral reactions may occur at any time after the drug is administered, but usually after the third day of treatment. Usually it is best to stop the drug, although in certain instances, when necessary, it can be continued with caution. Acute hemolytic anemia has not been observed by us, but others have reported the development of this condition. In such cases the drug should be discontinued and blood transfusions employed. Toxic reactions involving the white blood cells are essentially negligible in the treatment of uncomplicated cases of pneumonia. Occasionally a patient will develop leukopenia, but unless the drug is given for ten days or longer this condition should not cause undue apprehension. Obviously a progressive lowering of the white blood count with a decrease in polymorphonuclear cells below 40 per cent is to be respected, although the severity of the illness not infrequently prevents the stopping of the drug unless type specific serum is available.

Fever due to sulfadiazine may occur at any time, but usually after the fourth day. At times it is difficult to determine whether the temperature rise represents a drug reaction or a recrudescence of the infection. The fever of the original infection is usually normal by the third day of treatment, except when complications develop; if the patient is clinically improved, a secondary rise in temperature may usually be attributed to the drug. In such cases, if chemotherapy is stopped and fluids are forced, the temperature will drop within 24 to 36 hours. Whenever possible, it is best to discontinue chemotherapy in the presence of drug fever, as not infrequently this condition is followed by more serious toxic reactions. Psychoses due to sulfadiazine are difficult to evaluate in seriously ill pneumonia patients, but they do occur and, unless the infection is under control, there is no necessity to withdraw the drug.

Toxic reactions involving the urinary tract may occur with sulfadiazine at any time, but are most commonly seen after the fifth day of treatment. As mentioned before, the renal complications from sulfadiazine are due in part, if not entirely, to the presence in the urinary tract of crystals composed of the drug. However, the presence of crystalluria alone does not indicate renal involvement unless it is associated with progressing oliguria, hematuria, azotemia, or loin pain. In this study, approximately one-fourth of the sulfadiazine-treated patients showed crystals, presumably of the drug, in the urine. Microscopic hematuria was observed in 4.4 per cent of these patients, which is only slightly above the reported incidence of hematuria in cases of untreated pneumonia. Unless a considerable number of red blood cells are detected or other evidence of renal damage is apparent, cautious treatment may be continued; but it should be remembered that hematuria is often a precursor of severe renal insufficiency. Obviously, the appearance of gross hematuria is an indication for stopping the drug. Although no anuria, renal calculi, or loin pain was seen in this group of pneumonia cases treated with sulfadiazine, we have encountered these complications. In practically every instance in which a severe renal reaction to sulfadiazine has been observed, alkalis or adequate quantities of fluids had not been given and sulfadiazine had been administered over a period of four or more days. It is our impression that the relatively low incidence of renal complications in this series of sulfadiazine-treated cases may be related to the emphasis that was constantly placed on adequate fluid intake during drug therapy and the administration of alkalis. Should any of the kidney complications mentioned be encountered during sulfadiazine therapy, the treatment consists in prompt cessation of the drug, alkalization of the urine, forcing of fluids, administration of hypertonic dextrose solution to promote diuresis and ureteral catheterization, if necessary. The administration of mercurial compounds as diuretics or the use of magnesium sulfate as a cathartic is contraindicated in such cases.

Contraindications to Sulfadiazine Therapy

Theoretically, the only possible contraindication to the use of sulfadiazine in pneumococcic pneumonia is a history of a previous sensitivity to one of the sulfonamide compounds. However, in our experience there have been a number of patients who have developed toxic reactions to one of these drugs and not to another member of this group of compounds, although this would not necessarily indicate that the patient would not have had a toxic reaction if the original drug was used again. If a history of previous drug toxicity was obtained and the patient required immediate specific treatment, it has been our practice to use chemotherapy at once and follow the patient very closely for possible drug toxicity, rather than delay specific treatment until the administration of serum was made possible. In such cases we selected the drug least likely to cause the same type of toxic reaction (Table 3). It is too early to say whether the widespread use of the sulfonamides will result in an increasing number of patients developing sensitivity to these drugs, but, in view of the frequency with which pneumococcic pneumonia recurs, this problem merits further consideration. In a series of 24 adults having recurrent pneumococcic pneumonia treated with sulfapyridine, sulfathiazole, or sulfadiazine on two or more occasions, there was no evidence to suggest that the repeated use of these compounds had influenced the incidence or severity of drug toxicity. The presence of jaundice, acute nephritis, anemia, leukopenia, or neutropenia *per se* in a pneumonia patient does not contraindicate drug therapy, as these conditions will usually disappear as the infection is brought under control by adequate sulfadiazine treatment. Obviously, if such conditions are present, necessary measures should be taken to detect their further development.

Management of Complications

The presence of pus in a lesion prevents the sulfonamides from acting on bacteria with the same maximum effect which they exhibit in diffuse, nonsuppurating infections. Sulfadiazine,

therefore, is not to be employed as a substitute for surgical procedures in complications from pneumonia, such as empyema or abscesses, although the drug may be used in the hope of preventing a spread of the infection. Usually, in cases of massive pleural effusion, chemotherapy and thoracentesis will prove sufficient; but, if the effusion is thick and purulent, surgical intervention is indicated. Not only is the early diagnosis of pus-containing lesions in cases of pneumonia of great importance as an aid in treatment but also the incidence of severe drug reactions is greater in patients receiving chemotherapy over long periods of time.

Type-Specific Serum

For the most part the rôle of type-specific serum in the treatment of pneumococcic pneumonia remains a controversial subject. Certainly there is no clinical basis for its routine use, although there are certain pneumonia cases which are benefited by the administration of serum in combination with chemotherapy. For the most part we have limited the use of serum alone to cases in which severe drug reactions prevented the further use of chemotherapy, and of serum-plus drug in cases that failed to respond satisfactorily to the drug within 24 to 48 hours. On this basis, type-specific serum was employed in 124 (7.6 per cent) of our cases (Table 4) with a mortality of 37.9 per cent. Whether the successfully treated patients in this subgroup would not have recovered without the additional use of serum, we cannot say. There were, however, a number of seriously ill patients who showed a prompt clinical response after serotherapy. Not infrequently, serum was employed in cases with serious antecedent and/or complicating diseases with little or no expectation of its being effective. Unfortunately, concentrated efforts were not made to determine which of the cases in the combined therapy group represented drug-fast infections or failures in immunity response. Obviously, these two factors constitute the basis for the rational use of serum in those cases failing to respond to chemotherapy. No doubt, with the development of more accurate methods to evaluate these factors, the

employment of type-specific serum will play a more definite rôle. At the present time, it seems reasonable to use serum for patients unable to tolerate the drug and patients failing to respond to chemotherapy. When administering serum, the usual preliminary sensitivity tests, conjunctival and intradermal, must always

TABLE 4—COMBINED THERAPY CASES

<i>Type</i>	<i>All Cases</i>		<i>Bacteremic Cases (45.9 per cent)</i>	
	<i>Number</i>	<i>Deaths</i>	<i>Number</i>	<i>Deaths</i>
1... ..	29	7	18	4
2	8	2	2	1
3 .. .	25	14	8	5
4 .. .	12	7	11	7
7 .. .	18	5	7	4
8... ..	9	3	1	..
Others ..	23	9	10	7
Total... ..	124	47	57	28
Mortality, per cent	37.9		49.1	

(Flippin, H. F., et al., *J. A. M. A.*)

be performed. If these prove negative after 20 minutes, further intravenous testing with undiluted serum (1 cc.) is carried out. If, after 70 minutes, no untoward reaction has occurred, the patient is given an initial dose of 100,000 units of undiluted serum intravenously, followed by further injections when necessary. In general, if serum is beneficial, the patient will respond to 300,000 units or less.

Laboratory Procedures

The employment of certain laboratory procedures is of great importance in the diagnosis and treatment of pneumococcic pneumonia. In every case there should be adequate bacteriologic studies to determine the type of pneumococcus responsible for the infection. It is true that in most cases of pneumonia this information is of no therapeutic value, but in instances in which type-specific serum is indicated, a knowledge of the pneumo-

coccus type is indispensable. Blood cultures should be obtained as soon as possible. As already mentioned, if an antisulfonamide substance, paraaminobenzoic acid (5 mg. per 100 cc. of medium) is added to the culture material, the inhibitory action of the sulfonamide will be neutralized. This procedure should be adhered to whenever the patient has received even small doses of any sulfonamide. The sputum should be studied to determine the pneumococcus type, but in cases in which there has been some delay in typing, and the blood culture is positive, this examination is not necessary.

A blood count, including hemoglobin determination, leukocyte count, and a differential enumeration of the white blood cells should be done, preferably before the institution of drug therapy. It is best to check these blood constituents every two or three days, especially in cases in which the drug is required for longer than ten days. There is no absolute relationship between the number of leukocytes and the severity of the infection. In general, a high initial white count, which diminishes rather rapidly after 48 hours of treatment with the drug, is of good prognostic import, while a persistent or progressively high count often indicates a spread in the infection or a complication. Patients with low initial white counts are often seriously ill, but if they respond to treatment the count will usually increase within 48 hours. The failure of a low white cell count to rise is generally a poor prognostic sign.

Because of the potential dangers of sulfadiazine to the urinary tract, it is important to watch every patient closely for evidence of renal damage. The total amount of urine voided in each 24-hour period should be recorded, as well as gross and microscopic urine studies daily, to detect any evidence of kidney irritation. Blood urea nitrogen or nonprotein nitrogen determinations should also be performed in cases in which there are diminishing urinary outputs, and serum chlorides should be determined in cases in which appreciable quantities of fluid and electrolyte are lost. In most instances, it is not necessary to determine the blood concentration of sulfadiazine. However, in cases failing to re-

spond satisfactorily to the drug or with diminishing urinary outputs, it is practical to ascertain the amount of drug in the circulating blood.

The following plan of sulfadiazine treatment of pneumococcic pneumonia is suggested:

1. Early treatment.
2. Adequate chemotherapy:
 - (a) Large initial dose.
 - (b) Smaller doses at regular intervals.
 - (c) Continuation of drug until convalescence is established.
3. Maintenance of adequate urinary output.
4. Routine use of alkalis.
5. Prompt recognition of drug toxicity.
6. Determination of specific pneumococcus type.
7. Employment of other therapeutic measures as necessary:
 - (a) General supportive treatment
 - (b) Type specific serum.
 - (c) Surgical procedures.

* * * *

Long, Bliss, and Ott² reported on the treatment of 105 cases of pneumonia. Of these, 30 received sulfadiazine and type-specific serum, and 75 received sulfadiazine alone. Fifty-six of the 75 had pneumonia due to types I to VIII, 7 had bacteremia, 8 had complications associated with pneumonia, and 14 had a major concurrent disease. The response to therapy was usually prompt, but depended upon blood concentration during the first 12 to 24 hours. Only 17 of their series of 230 patients receiving sulfadiazine (various bacterial infections beside the cases of pneumonia) had toxic reactions.

However, although sulfadiazine is much safer than sulfapyridine, it is not free from danger, as has been indicated and as is pointed out by Fetter.³

It was originally thought that the undesirable renal complications, hematuria, renal colic, anuria, and uremia, would be much less frequent with sulfadiazine than with sulfathiazole, because of the lower acetylation of sulfadiazine, and the greater solubility of acetylsulfadiazine in the urine. However, these hopes

have not been borne out. All of these complications, including deaths from anuria, have occurred with sulfadiazine. Furthermore, the New York Department of Health has recently decided not to renew the supply of sulfadiazine to laboratory supply stations for the treatment of pneumococcal infections. This decision is based on the fact that as good results are obtained with sulfathiazole, which costs much less, and which probably produces only a few more toxic reactions.

TABLE 5—INCIDENCE OF TOXIC REACTIONS

<i>Reaction</i>	<i>Incidence With Sulfapyridine</i>	<i>Incidence With Sulfathiazole</i>
Vomiting . . .	47.0	10.0
Hematuria . . .	7.0	6.0
Anemia	5.0	5.0
Leukopenia	1.7	1.1
Drug fever	3.0	8.0
Conjunctivitis.	.	2.6
Dermatitis	2.6	4.2

(Fetter, F. U. S. Naval Med. Bull.)

The present status of sulfapyridine, sulfathiazole, and sulfadiazine in the treatment of pneumonia may be summed up as follows: The mortality rates are similar enough that there is no drug of choice on the basis of a lower mortality. Because of the much higher incidence of vomiting with sulfapyridine than with the other two drugs, it has been pretty well abandoned, and should be used only if one of the other two is not available. If cost need not be considered, and sulfadiazine is available, it is the drug of choice, but it produces toxic reactions often enough so that the same precautions must be taken with it as with sulfathiazole. If cost must be considered, sulfathiazole is the drug of choice.

This author's treatment follows: In addition to the sulfonamides, which were used in all but one case, oxygen was used in 120 cases (a little less than one-third of the patients), blood transfusions were used in nine cases, and serum was used in eight

cases. Of the sulfonamides, sulfapyridine was used in 115 cases, sulfathiazole was used in 270 cases (including five who received serum), and sulfadiazine was used in two cases (who also received serum). As a means of forestalling toxic reactions from these drugs, blood counts, urinalyses, and blood-sulfonamide levels were done three times a week, and a urinary output of at least 1200 cc. each 24 hours was insisted upon. Table 5 summarizes the undesirable reactions from sulfapyridine and sulfathiazole.

In three of the patients who developed hematuria (two treated with sulfapyridine and one with sulfathiazole), cystoscopy with ureteral lavage was necessary because of oliguria; all of these patients recovered. Anemia from the drug was considered present if the hemoglobin fell below 9.5 Gm., and leukopenia if the white blood count fell below 3500. The development of either of these conditions was considered an indication for stopping the drug.

Aside from the high incidence of vomiting from sulfapyridine, the number of toxic reactions with both drugs was relatively small. None of the deaths was attributable, even in part, to the drug.

Serum: Specific antipneumococcus rabbit serum was used in eight patients. In six of these it was given because the patient failed to improve and remained seriously ill after 24 to 48 hours' treatment with a sulfonamide. In one patient a persistent leukopenia (the initial white blood count was 1750) was an additional indication for serum, which was started 18 hours after failure to improve with sulfathiazole. In the last case, serum was given instead of sulfathiazole because the patient had aplastic anemia from benzene poisoning before the development of the pneumonia. Table 6 summarizes the cases treated with serum.

Deaths: Of the 388 patients, 35 died, a mortality rate of nine per cent. Six of these 35 patients died in less than 24 hours after admission to the hospital. If these are excluded the number of deaths is 29 and the mortality rate is 7.5 per cent. All deaths were in veterans and none was in active-service patients. Autop-

TABLE 6—PNEUMONIA CASES TREATED WITH SERUM

Type of <i>Pneumococcus</i>	Blood Culture	Indication for Serum	Total Serum Units	Result
1	Negative	Failure to improve with sulfonamide	410,000	Cure.
1	Positive	do	220,000	Do.
1	Negative	do.	80,000	Do.
1	do	do	200,000	Do.
1	Positive	do	200,000	Do.
1	Negative	do.	320,000	Do.
4	Positive	Failure to improve with sulfonamide, and leukopenia (WBC 1750)	200,000	Death
14	Negative	Aplastic anemia (WBC 2000)	140,000	Cure.

(Fetter, F. U. S. Naval Med. Bull.)

sies were performed in 17 cases, slightly less than half of the deaths. Table 7 summarizes the mortality rates with the various kinds of treatment.

Factors Influencing Mortality: The mortality rate is seen to be lower with sulfathiazole than with sulfapyridine. However, one cannot jump to the conclusion that the former drug is more effective than the latter, as the types of patients treated with the two drugs were somewhat different. Sulfapyridine was used during the first eight months of 1941, when the great majority of

TABLE 7—MORTALITY WITH VARIOUS KINDS OF TREATMENT

Treatment	Number Cases	Number Deaths	Mortality Rate (uncorrected)	Number Deaths Within 24 Hours	Mortality Rate Excluding 24-Hour Deaths
All types	388	35	per cent 9.0	6	per cent 7.5
Sulfapyridine	115	15	13.0	3	10.4
Sulfathiazole. . .	265	19	7.1	3	6.0
Serum and sulfonamide*	8	1	12.5		

*One of these patients, the aplastic anemia case, received serum only.

(Fetter, F. U. S. Naval Med. Bull.)

patients were veterans who were in the older age group. After September, 1941, when sulfathiazole was used, the number of younger active-service patients increased up to more than half the total. Further, it should be recalled that all of our deaths occurred in veterans. The mortality from pneumonia in naval service patients has been much lower than in the population at large, doubtless due to the facts that the patients come from the younger age group and are a selected group of particularly healthy individuals to begin with. This low mortality is shown in Table 8, the data for which were taken from the Statistics of Diseases and Injuries in the Navy for 1940.

TABLE 8—PNEUMONIA STATISTICS IN THE NAVY FOR 1940

<i>Form</i>	<i>Number of cases</i>	<i>Deaths</i>	<i>Mortality rate</i>	<i>Average of preceding 9 years</i>
			<i>per cent</i>	<i>per cent</i>
Lobar	367	10	2.7	15.8
Broncho	216	6	2.8	11.7
Total	583	16	2.7	

(Fetter, F • U. S. Naval Med. Bull.)

Navy statistics show further that while pneumonia and influenza, which are grouped together, were the third commonest cause of death in 1936, they had dropped to seventh place in 1940.

Before the introduction of the sulfonamides it was previously healthy young adults who were apt to die of pneumonia. Now it has been found that most deaths occur in infants under one year of age and in adults over 50 years. The youngest patient in our series to die was 43 years and 19 of the 35 deaths occurred in patients over 50 years.

In addition to the age factor, the presence of complicating diseases has an adverse effect on the mortality from pneumonia. Some complicating disease was present in all but four of the 35 deaths in this series. These are summarized in Table 9.

TABLE 9—COMPLICATING DISEASES IN FATAL CASES

<i>Complicating disease</i>	<i>Number of cases</i>
Heart disease.	13
Alcoholism.	8
Cerebral vascular accident.	3
Bronchial asthma.	3
Bronchiectasis.	2
Empyema.	1
Cirrhosis of liver with hematemesis.	1
None.	4
Total.	35

(Fetter, F.: *U. S. Naval Med. Bull.*)

Bacteremia has also been considered an important factor in pneumonia mortality. Stahle⁴ found the mortality rate in bacteremic cases to be three times that in the nonbacteremic (29.5 per cent and 9.2 per cent), and in Flippin, Reinhold, and Schwartz's⁵ series of 400 patients the mortality rate in the bacteremic patients was very high, 42 per cent. In Stahle's series, however, only 3 out of 23 patients with positive blood cultures died, giving a mortality rate of 13 per cent, which is only a little higher than the general mortality rate of nine per cent. However, the small number of bacteremic patients in this series makes these findings less conclusive than those in larger series.

REFERENCES

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- 2 LONG, P. H.; BLISS, E. A., AND OTT, E.: Bull. Johns Hopkins Hosp. 69: 297 (Oct) 1941.
- 3 FETTER, F.: U. S. Naval Med. Bull. 41:653 (May) 1943.
- 4 STAHL, D. C.: J. A. M. A. 118:440 (Feb. 7) 1912.
- 5 FLIPPIN, H. F.; ROSE, S. B.; SCHWARTZ, L., AND DOMM, A. H.: Am. J. M. Sc 201:585 (April) 1941.

PSITTACOSIS

While reports are very meager, there is some evidence that the sulfonamides are effective against psittacosis. The present belief is that parrot fever is a virus disease and the general rule is that the sulfonamides are ineffective against diseases caused by the viruses but this may be a notable exception. In any case, since the disease has a mortality of approximately 30 per cent and since there is no specific treatment against it, it would seem worth while to give sulfanilamide or sulfadiazine a trial.



PUERPERAL INFECTION

In no disease, says Brown,¹ does prophylaxis play a more important rôle. Here, preëminently, is illustrated the wisdom of the proverbial ounce of prevention.

Much in a preventive line can be done during pregnancy to get the woman into perfect condition for the risks of labor. Local diseases, such as vulvitis, cervicitis, otitis media, and sinusitis, should be cleared up well if possible before labor supervenes. Appropriate treatment for such general diseases as diabetes mellitus, syphilis, heart disease, etc., is of course obvious, but sometimes neglected. Especially is it important to clear up secondary anemia, which is common in the last trimester. If the hemoglobin is below 60 per cent the patient should be transfused before labor.

In labor the number of internal examinations should be limited to an irreducible minimum. The conduct of labor should be controlled, so far as possible, by external and rectal examination. During labor the woman's reserves should be protected by getting her sufficient sleep, rest, food, and liquids. Obstetric shock may follow a protracted labor, one in which exhaustion, starvation, and dehydration combine to reduce resistance, and sepsis may be lighted up. Just as important is the prevention of bleeding during labor.

In recognition of the frequency of air-borne infections and of the corollary that the source of many of these is the air passages of the attendants, masking of the nose and mouth should be

insisted upon. In most modern institutions this rule is among the regulations, but too often it is not abided by. For the same reason, if the patient should have an upper respiratory infection, she should also be masked. Colebrook aptly warns of the danger that less care may be taken with the antiseptic ritual since the introduction of the sulfonamides.

In the second stage, early episiotomy often prevents the occurrence of irregular, ragged tears. Many of us are often prone to use low forceps before the head has "ironed out" the pelvic floor and perineum. On the other hand, allowing the head to pound on a rigid pelvic floor for hours frequently harms both the mother and child.

The third stage should be conducted as physiologically as possible. Great care should be taken to obtain the placenta and membranes complete, as retained portions of either serve as an excellent culture medium for organisms that happen to be present. If a piece of placenta is missing, it should be removed manually at the time. If the major portion of the membranes is retained, this also should be removed. It is now customary to give a routine dose of some oxytocic to insure the uterus remaining firmly contracted for several hours after delivery. A firm uterus is an excellent barrier against bacterial invasion.

Repair of all lacerations of the perineum and vagina is important, and, if there is any reason to suspect laceration of the cervix, this should be inspected and sutured if necessary.

When careful examination has excluded all other causes for the illness and a diagnosis of puerperal infection is made, the woman should be isolated in the lightest, airiest room available, and every attempt made to put her at complete mental and physical rest. Her bed is placed in the Fowler position. General supportive treatment provides adequate diet, elimination, relief of pain, etc. The use of ergot for several days helps in keeping the uterus contracted. Culture of the lochia, taken from the vagina, should be sent for bacteriologic analysis. Developments may then be awaited. The days of active local treatment, as with intrauterine douches, strong antiseptics, and curettage, are gone.

The only permissible indication for local treatment should be the use of iodoform packing in case of intractable uterine bleeding.

As to specific treatment, the results of the use of vaccines, sera, and foreign protein therapy, on the whole, have been quite disappointing. The use of frequently repeated transfusions of 200 or 300 cc. of blood every two or three days is now well established and of real benefit. Use of blood from a donor who has recovered from a similar infection is of even greater benefit when available.

It is in the field of chemotherapy that the most important recent advances have been made. Colebrook's report in 1936 on the use of prontosil in 38 cases of puerperal hemolytic streptococcal infection with only three deaths was the forerunner of the widespread employment of the sulfonamide drugs in this type of infection, as well as numerous others. Probably the most brilliant results have been obtained with the use of sulfanilamide for patients infected with the hemolytic streptococcus. In many of these there existed an actual bacteremia, a condition formerly almost always fatal. What a hopeless feeling it was to read the laboratory report, "blood culture positive for hemolytic streptococcus," practically a death sentence. But now such a report on an ill patient, by contrast, is almost reassuring with sulfanilamide to fall back on. Particularly if the streptococcus is of the beta group is our drug more effective. The maximum initial dose (5 Gm.) should be given at once, particularly if the patient is acutely ill. This should be followed by 1 Gm. every four hours around the clock and continued until the temperature has been normal for five to seven days. We seek to maintain a blood concentration of 10 mg. per cent. Then the dose is tapered off over several days.

If cultures reveal the staphylococcus or *B. coli*, sulfathiazole may give us better results than sulfanilamide. Newer members of this group of drugs are constantly being experimented with, and it is hoped that some of the more recently developed drugs will provide greater protection against types of infection than

is now possible, and also that the toxicity will be reduced materially.

Occasional marked individual susceptibility to the toxic effects of various members of the sulfonamide group should give us real concern when administering these drugs. The toxic manifestations and the precautions to be observed in the course of therapy are well outlined in a recent article by Perrin H. Long and his associates. Since they are outstanding authorities on this subject, we can well afford to pay heed to the advice offered in some of the following quotations:

"Whenever possible, it is wise to utilize every available means of laboratory control in following patients who are receiving sulfanilamide or one of its derivatives. White blood cell counts, hemoglobin determinations, and urinalysis should be done whenever circumstances permit. However, with the exception of acute leukopenia, all the toxic manifestations of these drugs which may occur in the first two weeks of therapy can be recognized by careful clinical observation, and the authors feel that no physician should hesitate to administer these drugs in therapeutically adequate amounts, provided he can see his patient at least once a day.

"At the time the physician visits the patient who is receiving one of these drugs he should inquire as to his symptoms, especially in respect to headache, bodyaching, or malaise, because these symptoms are often the precursors of many of the toxic reactions. In addition, the sclerae should be examined for the presence of jaundice, the mucous membranes for pallor, and the skin for evidences of rash. The temperature should be taken several times a day to detect whether drug fever is present, and particularly is this important after chills.

"No special precautions have to be observed in respect to the urine of patients who are receiving sulfanilamide, but it is highly important that the urine of patients taking sulfapyridine or sulfathiazole be measured daily. In this way it is possible to detect an oliguria which heralds an approaching anuria.

"Finally, one should always remember that if a patient has once had drug fever, rash, hepatitis, leukopenia, acute hemolytic anemia, diarrhea, or purpura hemorrhagica in the course of therapy with sulfanilamide or its derivatives, he is likely to have a second, earlier, and more severe toxic reaction if the drug is administered a second time. Therefore, it is highly important to determine whether or not a patient has previously had a toxic reaction in the course of therapy with one or another of these drugs. If he gives a history of such a toxic reaction, it is best to give a small test dose of the drug (0.3 Gm.) and observe the patient carefully for 12 hours before cautiously beginning the course of therapy. Patients who have had a toxic reaction caused by one of these drugs may have a similar reaction when another member of the sulfonamide group is prescribed."

If these precautions are borne in mind the likelihood of unfortunate results with sulfonamide therapy will be rare and the advantages of this new addition to our armamentarium will be more fully realized.

REFERENCE

1. BROWN, RADFORD* *Med Annals Dist of Columbia* 12:15 (Jan.) 1943.



PYODERMA GANGRAENOSUM

See page 169



PYOGENIC DERMATOSIS

See page 173



PYURIA

See page 151



RESPIRATORY TRACT INFECTIONS¹

The introduction of any valuable new remedy is usually followed by a period of overenthusiasm regarding its use, then by a period of disillusionment, before it is finally given its rightful

place in the scheme of things. This sequence was evident after the introduction of quinine for malaria and of salvarsan for syphilis. Both drugs were, and still are, used for other infections for which they have no specific therapeutic value. This in itself is not in conformity with good medical practice, unless they are used as tests in a controlled experimental manner. In most cases no particular harm results except for the danger of toxic or untoward effects which may be caused by the drugs themselves.

A similar situation pertains to the use of the sulfonamide compounds, which at present appear to be enjoying the period of enthusiasm, so much so that they have recently been called "God's powder." It is still true that the sulfonamide compounds are of proved value only in infections caused by hemolytic streptococci, pneumococci, meningococci, gonococci, dysentery bacilli, in certain bacillary infections of the urinary tract, and in a few other infectious diseases, yet the chief indication for their widespread use seems to be fever, regardless of its cause. Because of certain inconveniences involved in making exact diagnoses according to cause, by which appropriate chemotherapy may be decided upon, there is indifference or reluctance to do so. Here again it is possible that no great harm may result in using sulfonamide routinely and empirically, but at present, until more facts are at hand, such practice should be rigorously discouraged. Besides their possible immediate toxic effects, no one as yet knows the extent and gravity of the danger which may arise from hypersensitivity after the use of sulfonamide compounds, if and when one of them is actually needed later for some serious infection.

The whole matter should be given serious consideration, because of the published advice to give the drug routinely in any mild infection of the respiratory tract to control the infection itself and to prevent the possible development of pneumonia. *It should be emphasized that no one has as yet proved that the common cold is amenable to chemotherapy.* Opinion is even divided as to the specific benefit of chemotherapy in uncomplicated pharyngitis or tonsillitis caused by the hemolytic

streptococcus. According to one observer, hemolytic streptococci actually developed in a patient who was receiving chemotherapy for another reason. Furthermore, it is a common failing to label any sore throat a "streptococcus throat" without an attempt to prove that the hemolytic streptococcus is the cause.

As far as preventing pneumonia in patients with colds is concerned, the value of chemoprophylaxis is equally uncertain. If only about one out of every 1000 patients with colds develops pneumonia, it seems hardly fair to subject the rest of them even to the apparently slight hazards of toxicity or sensitization to drugs. Then again, of the 0.1 per cent who *do* develop pneumonia, the disease will not in all cases be caused by the pneumococcus, and the value of sulfonamide chemotherapy for hemolytic streptococcic or staphylococcic pneumonia is far from being proved. And it is of no value whatever in pneumonias caused by viruses. In the present season, for example, about 75 cent of the pneumonias have been caused by agents other than those amenable to chemotherapy, and in many cases where chemotherapy was not used the mortality was nil. Circumstances may, however, change at any time; an epidemic of pneumococcic pneumonia may develop which urgently requires chemotherapy. On clinical grounds alone it is usually possible to differentiate typical pneumococcic lobar pneumonia from the atypical forms in which chemotherapy is of no avail. But the keystone of intelligent treatment of acute infections of the respiratory tract with sulfonamide compounds rests on accurate etiologic diagnosis and good clinical judgment. It is discouraging to learn from a recent investigation on the diagnosis of pneumonia that in only 17 per cent of cases were any attempts made to discover the causative organism. Such indifference is not consistent with good medical practice.

Until controlled investigation proves the harmlessness of indiscriminate sulfonamide therapy, or its beneficial effects either in controlling the common cold or mild infections of the respiratory tract, or in preventing the development of pneumonia in such cases, it should not be used routinely. The possible benefits

of its use in this manner must be carefully weighed against the possible harmful effects of the drugs themselves. They are, however, a few circumstances when sulfonamide compounds may be helpful as chemoprophylaxis in mild respiratory tract infections: (1) If some serious infection caused by bacteria sensitive to sulfonamide compounds, such as pneumococcic pneumonia or meningococcic meningitis, is also prevalent; (2) in obstetric patients at or near term; and (3) in patients with cardiac valvular lesions to prevent the development of subacute bacterial endocarditis, in spite of the doubtful effect of the sulfonamide compounds on the *Streptococcus viridans*.

Chemotherapy may be used empirically in the occasional case of pneumonia of doubtful cause if facilities are not available for laboratory studies, and in severe cases of sore throat caused by the hemolytic streptococcus with lymphadenopathy and threatened or actual septicemia.

REFERENCE

- 1 Editorial Penna M. J. 46:719 (April) 1943.



RHEUMATIC FEVER

See pages 6 and 150



ROSENBAACH'S ERYSIPELOID

See page 168



ACUTE SALPINGITIS

Sulfathiazole and sulfanilamide were used alternately by Barrows and Labate¹ in the treatment of 71 patients with their first attacks of acute salpingitis and 133 patients during an acute exacerbation of chronic salpingitis. Gonococcic cervicitis and urethritis made a good response to sulfonamide therapy. All of the previous positive smears became negative after treatment.

However, the effectiveness of chemotherapy on gonococcic lesions above the level of the internal os is dependent directly upon the duration of the disease before treatment is instituted and upon the extent of the tubal damage which has been incurred. In 70 per cent of the patients with mild attacks and in 66 per cent of those with a moderate initial attack of less than five days, complete resolution of adnexal masses occurred within one week after the beginning of chemotherapy. There was no adequate response of primary salpingitis which had a duration of more than five days nor of recurrent salpingitis in the moderate or severe groups. Permanent damage of the fallopian tubes may be prevented or minimized if sulfonamide therapy is begun within five days of an initial attack of adnexal disease.

REFERENCE

1. HARROWS, D. N., AND LABATE, J. S. *Am. J. Obstet. & Gyn.* 45:82 (Jan.) 1913.



RHINITIS

See Common Cold, pages 6 and 161



SCARLET FEVER

See pages 6 and 152



SERPENT ULCER OF EYE

See page 266



SINUSITIS

See page 278



SINUS SURGERY

Littell¹ reports on the local use of undiluted sulfonamide drugs in sinus surgery.

About a year ago it occurred to the writer that the sulfonamides in pure form might play a very useful part in preventing reactionary inflammation in the raw surfaces created by sinus surgery. Here there are more or less large areas of bone, denuded of infected mucoperiosteum, lying exposed in a necessarily infected field. Our effort has been to use it on these raw surfaces only, as in the denuded bone following ethmoidectomy, where there is a considerable area of this kind.

This report covers observations on 80 cases of partial or complete ethmoidectomy, of which 39 were bilateral. These were all intranasal operations except three which were external, and all presented a considerable raw infected surface on which the powder was used. The drug was omitted in the uncomplicated submucous operation, as there is only a minimal exposed raw surface presented following this operation. The use of the powder on the mucous membrane of the nose has seemed to us to result in a reactionary inflammation of a definite degree (its high pH), as demonstrated by blowing the powder into one side of the nose, having the other untreated side as a control, in the office care of nasal infection. For this reason its use was confined to raw surfaces only.

Its effect on the denuded bone of the ethmoid has apparently been favorable. These cases have seemed to do exceptionally well. The surgical reactions have been minimal and ease for ease much less than would appear to be expected for the given degree of pathology. Ethmoidectomies done during the less favorable months of the year, or when a somewhat more active inflammatory state than perfectly desirable prevailed, have been afebrile and amazingly comfortable from the first day on. Furthermore, almost invariably they have seemed to bleed less during the six hours following surgery than before.

Instead of impregnating gauze with the powder, as Kern does, our custom has been to blow it on to whatever area we desire with the powder blower. The drug is then in intimate contact with the entire bare area and remains there. Perhaps the gauze-impregnated packing is better, and I shall be glad to try it, but

it would seem reasonable to suppose that the drug would be much more readily available to the tissue when blown on to it, for here we have an uninterrupted carpet of the drug filling every surface irregularity, whereas with the packing there would be tissue contact with it only in very occasional and irregular fashion. This is particularly true when one folds the vaseline packing in quite loosely, as we do, with very little contact anywhere.

The use of the blower also allows one to avoid packing if he chooses. We usually find it unnecessary to use packing of any kind in nasal or sinus surgery, except a light pack for a submucous operation to prevent a hematoma, or to serve as a matrix for a clot if the patient shows more than the average tendency to bleed. We have no quarrel with those who prefer a light pack elsewhere, but simply feel it is usually unnecessary, as the patient is much happier without it, and the results are at least as good. The powder has seemed helpful in postoperative exuberant granulations in the nose, hastening their disappearance and causing no reaction if the drug is limited to the granulation surface only.

Sulfanilamide powder was used in the first 20 cases, after which sodium sulfathiazole powder was substituted. It was thought that this drug might control a larger proportion of the prevailing microorganisms found in this area. The results, however, were not noticeably different. There was one disadvantage in that the powder of the latter drug proved to have a somewhat flocculent character, and it was more difficult to maintain the patency of the powder blower. Since midsummer we have used sulfathiazole crystals which we further pulverized in a mortar. These particles remain more discrete, do not clump, as does the powder, and coat the raw surface evenly.

We realize that the above is concerned with clinical observations, in contradistinction to the research methods of the laboratory, but the results seem of such a definite nature as to justify and encourage further trial of these drugs in the fields suggested, as well as perhaps associated fields. The series is not large and,

as in the case with any new drug or method, enthusiasm should be restrained until our observations have stood the test that time imposes. The use of these drugs should not make us feel privileged to take undue surgical risks with the hope that their use will cover up or mitigate any mistakes in judgment. But, whether or not it is justified, I cannot help sharing Kern's feeling of security when the undiluted sulfonamide drugs are used following nasal surgery.

REFERENCE

1. LITTELL, J. J. FROME. Jour Indiana State Med. Assn. 36:250 (May) 1943.



SMALLPOX

Wilkinson¹ treated 13 toxic cases of smallpox with sulfanilamide, giving 1 Gm. every four hours day and night, with the usual modifications for children. Ten of the cases were unvaccinated and three showed good vaccinal scars. Twelve were admitted to the hospital on or before the sixth day of the disease. On the average these cases lived 3½ days, so that the drug did not have long to act, but the natural course of the disease was not modified in the least.

Forty-nine patients in the focal phase, unvaccinated, received the same dosage of sulfanilamide. In 19 of these the vesicles, instead of developing into mature pustules, dried up and left the face covered with a multitude of small horny pocks resembling the horn-pock condition so often seen in well-modified smallpox. In these 19 cases the secondary focal or septic fever was either annulled or diminished.

In the focal phase, vaccinated, there were 41 patients who received sulfanilamide for some septic complication, the commonest being boils, muscle abscesses, skin sloughing, cellulitis, and otitis media. Rarer complications were panophthalmitis, suppurative arthritis or periostitis, and streptococcal infections of the urinary tract. It was in these complications that sulfanilamide proved most valuable. In no case was the drug started until the complication had developed. Local antiseptic dressings

were used once drainage of an abscess was established, and recovery was always prompt and uninterrupted providing sulfanilamide was given in adequate dosage.

Of the total of 103 patients treated with sulfanilamide during this epidemic 26 died, a fatality of approximately 25 per cent, against a fatality of 44 per cent for the entire epidemic.

REFERENCE

1. WILKINSON, P. B.: The Lancet (London) 2:67 (July 18) 1942.



STREPTOCOCCUS VIRIDANS SEPTICEMIA

Tannenbaum¹ reports a case of streptococcus viridans septicemia cured with sulfapyridine. The diagnosis was established by four positive blood cultures. The patient was discharged from the hospital cured, as evidenced by six negative blood cultures and by normal physical and laboratory examinations.

Treatment was started with 4 Gm. of sulfathiazole, followed by 1 Gm. every four hours. Pericarditis and endocarditis developed and treatment was then switched to sodium sulfapyridine intravenously. Six Gm. were given in 150 cc. of sterile distilled water twice daily in addition to 1 Gm. by mouth every four hours. Additional therapy consisted of whole blood, dextrose, and physiologic saline solution. The blood sulfapyridine concentration reached 16 mg. per 100 cc. After four days the temperature was within normal limits. Examination six months after the onset of the illness revealed no abnormal physical or laboratory findings.

REFERENCE

1. TANNENBAUM, A. J.: J. A. M. A 118:372 (Jan. 31) 1942.



STYE (PERIFOLLICULITIS; HORDEOLUM)

Sella¹ reports the use of sulfathiazole in sty, with cure in from two to four days. He gives 0.03 to 0.04 Gm. per kg. of body weight orally for from six to nine days.

However, in such a minor infection as sty, it scarcely seems like good therapy to subject the patient in ordinary circum-

stances to the dangers of toxic reactions from the sulfonamide drugs.

REFERENCE

- 1 SELLA, E: Med. Espanola, Valencia 8:498 (Nov.) 1942.



SURGICAL INFECTIONS

Veal and Klepser¹ report on the use of sulfanilamide in 300 infected wounds, including infected burns, compound fractures, leg ulcers, decubital ulcers, localized abscesses, and carbuncles. Powdered sulfanilamide was used in the early stages of these conditions, and, as soon as bacterial growth and the exudate had diminished and the inflammation had subsided, the daily application of powdered sulfanilamide was replaced by the daily application, over the entire lesion, of a thin layer of sulfanilallantoin ointment. This was covered with a dry gauze dressing.

Systemic toxic reactions or the cyanosis seen so frequently after the oral or the parenteral administration of sulfanilamide was not observed in the patients treated locally. However, there was a cumulative rise of the level of sulfanilamide in the blood in certain patients given large daily doses over a long period.

The accepted rule for dosage in local application of sulfanilamide should be followed in these conditions. One Gm. is applied for each ten square inches of surface involved, but in closed cavities not more than 5 Gm. should be used. At no time should more than 15 Gm. be used locally, for the drug is absorbed readily and toxic reactions can readily develop.

REFERENCE

1. VEAL, J. R., AND KLEPSER, R. G.: Surgery 10 947 (Dec) 1941.



TONSILLITIS

See pages 8 and 153



TRACHOMA

See page 263

TRENCH MOUTH

Hirsch and Spingarn¹ found sulfathiazole effective in eight cases of fusospirochetal infections of the mouth and throat. Their report follows:

The patients with gingivitis were given 1 Gm. of sulfathiazole four times daily. Their mess gear and drinking glasses were isolated, but they were allowed to perform their usual duties. The lesions were inspected daily and smears were made and stained for organisms. No other treatment of any sort was given while the drug was being taken.

The patients with angina were confined to bed in an isolation ward and were given an initial dose of 2 Gm. of sulfathiazole, followed by 1 Gm. every four hours during the day only. In addition, they were given throat irrigations two or three times daily. (In one case, sodium perborate was used; in the other, saline solution.)

In each group treatment was stopped when the fusiform bacilli and spirochetes had almost completely disappeared from the smears (within two to six days).

In the six cases of gingivitis symptomatic relief was obtained within 24 hours after the sulfathiazole was started. The patients stated that the gums were no longer sore and that they could brush their teeth with less pain and bleeding. Removal of the exudate from the interdental papillae by means of a cotton swab after 48 to 72 hours of treatment did not cause bleeding and revealed pink, healthy-looking gingival tissue. The daily smears of the affected areas showed a striking decrease in the number of Vincent's organisms after 24 hours of treatment (4 Gm. of sulfathiazole) and the almost complete disappearance of these bacteria from the smear where treatment was stopped within two to six days. Follow-up examinations one to four weeks after the cessation of the drug failed to reveal any evidence of a recurrence.

In the two cases with tonsillar or pharyngeal involvement, the response to sulfathiazole was prompt. In the first case, the infec-

tion had produced a deep ulceration of the left tonsil (auto-tonsillectomy), which was associated with extreme dysphagia, malaise, and a temperature of 100° F. (oral). On the fourth day of treatment, the peritonsillar swelling had subsided and smears from the depth of the ulcer crater revealed only an occasional spirochete. The temperature returned to normal within 24 hours and a tender cervical lymphadenitis subsided shortly thereafter.

The second patient was seen first with the typical findings of infectious mononucleosis, as indicated by the characteristic blood picture and a heterophile antibody titre of 1:1792 (report from the National Naval Medical Center). On the fifth day of this disease, he complained of severe dysphagia and, on examination, there were whitish patches on both fauces that extended to the uvula. The exudate was easily removed and on smear showed many spirochetes and fusiform bacilli. Throat irrigations with sodium perborate were instituted. There was no local improvement and the patient continued to have an elevated temperature. On the seventh day he was given sulfathiazole and within 48 hours the pharyngeal signs regressed, the temperature became normal, and the patient felt much improved.

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TUBERCULOSIS

The sulfonamide group of drugs gave much hope that the cure of tuberculosis was at hand. In fact, sulfanilamide and sulfathiazole appear to have some inhibiting effect on the development of experimental tuberculosis in guinea pigs.¹ Zucker, Pinner, and Hyman² gave sulfanilamide in large doses by intravenous drip to 13 patients with pulmonary tuberculosis without causing any change in the parenchymal lesions, although two mucosal tuberculous lesions, a pharyngeal ulcer, and an endobronchial lesion healed during the period of treatment.

A new sulfone drug, promin (sodium P,P'-diaminophenyl sulfone N-N' didextrose sulfonate), recently seemed to give

much promise. Various reports on the use of this drug^{3, 4, 5, 6} in experimental tuberculosis in guinea pigs gave indications that it is of value in preventing and arresting the infection. However, the results obtained in human tuberculosis were not as favorable. Zucker, Pinner, and Hyman,⁷ for instance, gave promin in large doses by continuous intravenous drip to 12 patients without bringing about any improvement in the parenchymal lesions, although, just as in their work with sulfanilamide, they brought about healing of a tracheobronchial ulcer.

A drawback to the use of promin is the high incidence of toxic reactions, particularly hemolytic anemia.⁸

Hinshaw, Pfuetze, and Feldman⁹ report on the treatment of 36 patients with promin. It is important, they say, to indicate some limitations of chemotherapy with promin as well as to suggest lines for further investigation. Evidence appears adequate to state that the drug, when administered as we have used it, will not sterilize the body promptly of tubercle bacilli and that late destructive terminal stages of tuberculosis are not influenced favorably. These late stages of tuberculosis are as different from early exudative infiltration as postpneumonic pulmonary abscess is unlike early pneumonia. In pneumococcic pneumonia and in other diseases amenable to chemotherapy early treatment is necessary to secure good results. If treatment is delayed until destruction of tissue occurs, the prompt, dramatic arrest of the infection is not to be expected. We cannot know at this time if there will be similar limitations to chemotherapy in tuberculosis, but this comparison should be kept in mind.

The failure of promin to cure tuberculous meningitis brings to mind the difficulties of treatment of pneumococcic meningitis, which necessitate much more intensive and more prolonged chemotherapy than is required in treatment of early pneumonia. The toxic properties of promin are too great to permit similar increase of dosage for treatment of tuberculous meningitis.

The successful treatment of experimental tuberculosis of guinea pigs with promin has been accomplished when treat-

ment was delayed for six weeks after infection. Biopsy of lesions in the liver at this time has demonstrated that simple discrete tubercles alone were present when treatment was started. Caseation necrosis with tissue destruction was not observed before treatment in these experiments. Such lesions may be comparable to recent pulmonary infiltrations in man. The clinical evidence suggests possible therapeutic effect, especially in those patients whose lesions are more comparable to those of guinea pigs and in which the tolerated dose more nearly approaches that of the animals.

Further trial of promin in treatment of pulmonary tuberculosis appears justified. The results obtained in the present report suggest that emphasis should be placed on study of recent lesions without evidence of destruction of tissue or extensive fibrosis and that treatment of terminal phases of the disease should not be encouraged.

If it is possible to modify the toxic and therapeutic properties of the sulfone series of drugs as favorably as has been accomplished for the sulfonamide series, we may anticipate further progress in clinical chemotherapy of tuberculosis.

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TULAREMIA

May¹ reports a case of late tularemic septicemia with recovery following medication with sulfonamide compounds. Treatment was started with prontosil 5 grains every three hours and 5 cc. of prontosil solution every four hours intramuscularly. A total dosage of 90 grains of prontosil and 75 cc. of prontosil was given over a three-day period. A dramatic drop in temperature occurred on the second day, the first fall in 12 days.

Richards² reports four cases of tularemia with pulmonary complications treated with sulfanilamide, the patients receiving from 60 to 90 grains a day. Additional therapy consisted of transfusions in two cases and convalescent serum in one. All the cases made complete recovery.

The mere fact that all of our cases with pulmonary complications recovered after receiving sulfanilamide, says the author, does not prove it to be a specific. The complications may have been owing to a secondary infection, but such organisms should have been easily recovered in the cultures made. The mortality rate in all cases of tularemia is low, but at least half the cases that die have pulmonary complications. The favorable response to sulfanilamide was so immediate and the patients had been sick so long that it precludes the possibility that the results were just a coincidence. Our conclusions were that the drug has definite therapeutic value in tularemia.

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TYPHOID FEVER

Various writers have reported that the sulfonamides are without value in the treatment of typhoid fever. In the treatment of typhoid carriers, however, opinion is not uniform regarding the use of sulfaguanidine. Levi and Willen¹ advocated the use of this drug in the carrier state. They administered 0.5 Gm.

per kg. ($3\frac{3}{4}$ grains per lb.) of body weight of sulfaguanidine every eight hours for one week to a biliary and intestinal typhoid carrier who underwent cholecystectomy before the drug was used. Cultures were taken of ten specimens of feces, three of them after the use of magnesium sulfate, and all gave negative results. These authors stated: "This method of therapy is worthy of further trial."

Saphir, Baer, and Plotke² reported on the treatment of five intestinal carriers with sulfaguanidine in a manner similar to that used by the above authors. The same dose was given four times a day for two weeks. "The results," they stated, "were uniformly unsatisfactory. In all cases in which treatment was given the bacillary excretion continued unabated."

Hoagland,³ on the other hand, had satisfactory results in two typhoid carriers treated with sulfaguanidine and gives the following case reports:

CASE 1—B. M., a girl aged 17 years of Japanese descent, was a healthy typhoid carrier to whom was traced a recent epidemic of typhoid occurring in a junior high school. The patient and her parents stated that she had never had typhoid. Her father, with whom she lived, also was discovered to be a typhoid carrier. Specimens of feces on four consecutive days were found to contain *E. typhosa*. The organism was agglutinated by an anti-typhoid serum in dilutions of the latter as high as 1:10,240.

She was admitted to the hospital on March 19, 1912, without clinical manifestations of disease. Laboratory investigations in this hospital consisted of blood, feces, urine, and biliary cultures. Cultures of one blood specimen and five urine specimens failed to reveal the presence of *E. typhosa*. Three specimens of bile obtained by the duodenal tube before the institution of treatment and three obtained after cessation of the second course of treatment were free of *E. typhosa*. The flow of bile was variously stimulated by magnesium sulfate, bile salts, and olive oil, because it was thought that the first named might have an inhibiting effect on the growth of *E. typhosa*. On March 31 sulfaguanidine 2 Gm. four times a day was administered, and on April 5

its administration was discontinued. Daily specimens after treatment ceased showed no *E. typhosa* until a specimen obtained on April 12 yielded typhoid bacilli on culture. It was then decided to institute another course of treatment with greater doses of the drug. Therefore, 4 Gm. of sulfaguanidine were given five times during the day, making a total daily dose of 20 Gm. The drug was given for a period of six days. Two specimens of feces were obtained while the patient was undergoing the second course of treatment. Cultures of both showed no *E. typhosa*. Cultures of feces specimens obtained on 14 occasions since cessation of the second course of treatment all failed to reveal *E. typhosa*. The last specimen was obtained 43 days after treatment. Three specimens of the patient's feces were obtained after stimulation of defecation by various cathartics—magnesium sulfate, cascara, and aloin were each used once. The blood level of sulfaguanidine during treatment was 2.48 mg. per 100 cc. At no time during either course of treatment did she have any clinical or laboratory manifestations of undesirable effects of therapy. Urinalyses and blood counts during and after treatment showed normal results.

CASE 2—D. H., a boy aged 14 years of Japanese descent, had been sick at home with mild typhoid, which was unrecognized until it was discovered that he had been the source of the only secondary case in the typhoid epidemic referred to in Case 1. He had no clinical manifestations of disease. His serum agglutinated *E. typhosa* in a dilution of 1:1280. Two cultures of bile and six of urine showed absence of *E. typhosa*. Treatment was instituted exactly as in Case 1. Urinalyses and blood counts during and after treatment gave normal results. The patient had five feces examinations before treatment, with the presence of *E. typhosa* demonstrated in each specimen. He had seven feces examinations after treatment (the last specimen was examined 17 days after treatment) with *E. typhosa* not demonstrable in any specimen.

Since we found⁴ that 60 children ill with typhoid all spontaneously ceased to eliminate *E. typhosa* in their feces, the ap-

parently successful result of treatment of D. II., a convalescent carrier, may have been adventitious. However, the abrupt cessation of constantly positive cultures was striking. Moreover, it is noteworthy that the same dosage of sulfaguanidine employed in Case 1 produced no clinical or laboratory manifestations of undesirable effects of therapy.

The author states that the dose of sulfaguanidine in the typhoid carrier state should be as high as 20 Gm. (300 grains) a day if smaller doses are ineffectual.

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ULCERATIVE COLITIS

Sulfonamide therapy gave great hope for a time that the means were at hand for the conquering of ulcerative colitis, but clinical results to a great extent have been disappointing. Streicher,¹ reporting on the management of 912 cases, states: "The introduction of therapy with sulfanilamide and its derivatives was received with relief, but, while almost miraculous results have been recorded in some isolated instances, use of these drugs in the treatment of chronic ulcerative colitis is hazardous.

"Their specificity of action on infections due to *Streptococcus hemolyticus* has been established, but, while a small percentage of patients with chronic ulcerative colitis do harbor this streptococcus, the predominant bacterium present in the stool and obtained on culture is *Streptococcus viridans*. Any beneficial results obtained with any of these compounds in the treatment of chronic ulcerative colitis must therefore be considered incidental or secondary, due to an indirect action of the drug."

The treatment recommended by this author follows:

- (a) Diet high in vitamins.
- (b) Powdered opium, dilute HCl, liver extract, phenobarbital at bedtime, ferrous sulfate.
- (c) Sulfanilamide derivatives.
- (d) Vaccine (polyvalent).
- (e) Removal of foci of infection.

The author's results with sulfanilamide were disappointing; with azosulfamide they were somewhat better. Sodium sulfathiazole in a dosage of 1 Gm. every four to six hours for seven days was the most advantageous.

The results achieved with sulfaguanidine in bacillary dysentery again seemed to offer promise that this drug might be just as effective in ulcerative colitis. However, Kirsner, Rodaniche, and Palmer² were unable to obtain any consistent therapeutic results with the drug, although it does decrease the bacterial content of the feces. Likewise, Stickey, Heilman, Bargaen, and Dearing³ felt that it was impossible to ascribe any consistent value to sulfaguanidine in treating ulcerative colitis.

More encouraging is the report of Svartz⁴ on the use of a new sulfa drug, salicylazosulfapyridine, in the treatment of five cases of ulcerative colitis. This drug appears to be the best available medicament against the disease. Two tablets of 0.5 Gm. each were given from four to six times daily and continued in gradually diminishing doses after symptoms subsided for about one month. Fever and rashes often accompany the administration of the drug but other complications are rare. The sulfapyridine constituent is the cause of the skin eruptions. Skin tests are of no value in the detection of hypersensitivity to either salicylazosulfapyridine or sulfapyridine, for patients who have given negative skin reactions have shown signs of hypersensitivity. Amino-pyridine, a substance which probably forms in the organism as the result of the cleavage of sulfapyridine, gives a positive cutaneous reaction in patients who have had an exanthem after medication with salicylazosulfapyridine.

Another new sulfa drug in the treatment of ulcerative colitis, succinylsulfathiazole, has been reported by Crohn.⁵ During a period of six months he administered this drug to 28 patients with ulcerative colitis, eight with ileitis or ileojejunitis, and one with intestinal actinomycosis. The dose given was 0.25 Gm. of the drug per kg. of body weight for ten days. After a lapse of five days a second series was given. When severe diarrhea is present, opium in some form should be administered concurrently in order to slow down intestinal movement and permit a concentration of the drug in the intestinal canal.

Toxic effects were few. Loss of appetite was common, but nausea and vomiting were rare. Occasionally the patient complained of headache or malaise and mild prostration.

Five patients with ulcerative colitis had an apparent and quick symptomatic cure and 11 more showed definite improvement.

While there are not yet sufficient clinical reports available to judge finally the effectiveness of this drug in ulcerative colitis, it gives promise of being a welcome addition to the armamentarium, since it apparently exhibits no toxic by-effects and can be pushed in large doses with relative impunity. Best results have been obtained in acute ulcerative colitis, so that it seems possible that with early diagnosis and intensive therapy with succinylsulfathiazole the entire picture of the lingering debilitating disease which is seen so often now may be completely altered.

One of the discouraging features of chronic ulcerative colitis has been its recurrent nature. Preventing these recurrences is just as important, if not more so, than bringing about a remission, and it is possible that the continuous use of this drug may solve this problem.

The situation with terminal ileitis is not so promising. Terminal ileitis is associated with delay in the distal loops of the small intestine, and a concentration of the drug at this point may overcome a pathologic process if the disease is really an infection.

The patient with actinomycosis and several fistulas to the abdominal wall showed definite improvement. Succinylsulfa thiazole caused the fistulas to dry up, the discharge diminished,

and the macerated dermal tissues of the abdominal wall underwent a definite stage of granulation.

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CHRONIC HEMOLYTIC STREPTOCOCCIC ULCERS OF THE EXTREMITIES

Taylor¹ reports on the use of sulfanilamide in chronic hemolytic streptococcic ulcers of the extremities. These ulcers usually will not heal with local treatment, but the oral use of sulfanilamide is specific. The drug is given in an initial dose of 3 to 5 Gm., followed by 1 Gm. every four hours night and day for six or seven days.

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UROLOGY

Sulfanilamide and its derivatives, says Pool,¹ are of little value in the sterilization of urine when the infective agent is the *Streptococcus fecalis*. *Pseudomonas aeruginosa* is particularly resistant to the sulfonamide derivatives.

For patients suffering with a urinary infection of a type for which a sulfanilamide derivative can be prescribed, he continues, we are now using sulfathiazole more than any other drug. We prefer to prescribe a relatively small dose, which usually is 1 Gm. (15 grains), taken three times per day. Administration of the drug is continued for seven to ten days, and if the urine is not sterile at the end of this time, either some other form of medication is prescribed or all medication is

stopped for the time being. If the urine is sterile, experience has shown that it is advisable to continue the medication for three or four extra days. Occasionally, patients will state that they cannot tolerate this dose, and in such a case a smaller dose can be tried. Very infrequently, administration of even the smaller doses may have to be discontinued and some other drug substituted.

Factors Causing Therapeutic Failure: The factors which can cause a therapeutic failure are easily understood. In a few cases the drug cannot be tolerated, or a toxic manifestation occurs; in such instances it is necessary to discontinue administration of the drug. Other factors which can cause failure are the presence of a tumor, a calculus, imperfect drainage of any part of the urinary tract, or marked involvement of the tissues with resulting cicatrization. Naturally, when any of these factors is present, a clinical miracle cannot be expected, nor can it be expected that an infected urine will become sterile. This fact has been expressed many times by Cook.

In cases in which there is long-standing, chronic infection, it occasionally becomes necessary to change the mode of administration of the drug. Frequently, the patient is asked to take the drug for the first week of each month under the supervision of a physician. At times it may be best to prescribe very small doses to be taken during a longer period. In prescribing the sulfamido derivatives in alternate courses, the physician should remember that toxic reactions are likely to occur if use of the drug is resumed within less than seven to ten days after it was discontinued. Why this is true cannot be readily explained. Perhaps it is best in some cases to alternate use of the drug with use of some other urinary antiseptic agent, such as mandelic acid.

Some of the greatest apprehensions confronting the physician caring for patients who have urinary infections have their source in the recurring bouts of acute infection which afflict certain of his patients. Usually, no focus of infection can be found, although among women the cervix frequently is suspected. When no focus of infection can be found, little can be done except to

administer to these patients some form of alternate therapy in the hope that the attacks will become less frequent until they eventually disappear. Braasch has used this method for many years.

Sulfanilamide as a Prophylactic Agent: The use of sulfanilamide as a prophylactic agent is an interesting practice which is now being evaluated. Emmett has shown that if small doses of sulfanilamide derivatives are administered during the post-operative period, they help to reduce the incidence of infections of the urinary tract among women who have undergone gynecologic operations. Thompson and Strom recently studied the effects of sulfathiazole administered during the preoperative and postoperative periods to patients undergoing transurethral prostatic resection. They concluded that the morbidity rate was decreased and that the complications usually encountered after this type of operation were less frequent after such treatment.

Also see Gonorrhea, page 212, and Chancroid, page 116.

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VULVOVAGINITIS

See page 132



WOUND INFECTIONS

In any consideration of the use of sulfonamide compounds in the prophylaxis or treatment of wound infection, says Long,¹ several factors must be considered, and among these are the type of surgical procedure employed, the condition of the wound at the completion of surgical treatment, the determination of whether oral and/or local sulfonamide therapy will be used, the proper selection of the drug for peroral or local use, the dosage to be used, the duration of treatment, and finally the utilization of the correct postoperative care in order that the

greatest benefits may be derived from the employment of the sulfonamide compounds.

It has been established that the sulfonamides can be used in the treatment of wounds, regardless of the type of surgical procedure that has been employed. As far as is known at the present time, the administration of these drugs is compatible with the use of standard intravenous, inhalant, or local anesthetics, and they will not influence adversely either the course or the treatment of traumatic or infectious shock.

The condition of the wound at the time sulfonamide therapy is used is of importance. Obviously a poorly débrided, carelessly drained fresh wound is an unsuitable site for the implantation of the sulfonamides, and under such conditions the drugs may eventually fail to exert their prophylactic effect. The method of wound closure is important. Implanted sulfonamide compounds may cause an exudation of tissue fluids into the wound, and sloughing of the wound edge has been noted as a result of the tension created by these fluids when wounds have been closed too tightly. This possibility should be kept in mind when one is dealing with lacerations in which especial consideration must be given to the final cosmetic effect. It has been shown that necrotic material or pus contains sulfonamide inhibitors, hence every effort should be made to eliminate and neutralize these substances before sulfonamide therapy is started.

The experience of the last few years has shown that oral, topical, or oral plus topical medication with the sulfonamides will prevent wound infection. However, the best evidence available at the present time shows that the administration of these drugs by the peroral and local routes is to be desired in the prophylaxis of infection in moderate or serious wounds of the soft tissue, compound fractures, compound skull or faciomaxillary injuries, and penetrating wounds of the abdomen or chest. Infection can generally be prevented in minor lacerations involving the skin and subcutaneous tissues or superficial muscle layers, without extensive destruction of tissue, by the topical application of a sulfonamide compound.

In the selection of the drug of choice for the peroral prophylaxis or therapy of wound infection, the effectiveness of the drug and its toxicity are primary considerations. It has been shown that sulfadiazine is clinically effective against systemic infections produced by staphylococci, hemolytic streptococci, colon bacilli, and members of the aerogenes group. In clostridial infections this drug has been proved active against experimental infections produced by *Clostridium perfringens* or *Clostridium septicum*. It offers a wide range of protection against the common primary contaminating and infecting organisms in wounds.

A recent survey which we have made of the occurrence of the important toxic reactions (fever, rash, acute hemolytic anemia, leukopenia, acute agranulocytosis, renal complications, and hepatitis) of sulfanilamide, sulfapyridine, sulfathiazole, and sulfadiazine shows that a total of 11.9 per cent of such reactions occurs in the course of sulfanilamide therapy, 15.9 per cent when sulfapyridine is employed, 18.6 per cent if sulfathiazole is used, and but 6.5 per cent when therapy is conducted with sulfadiazine.

In addition, sulfadiazine produces comparatively little nausea and vomiting and rarely any degree of cyanosis; mental disturbances and incoördination are uncommon; endurance is not seriously affected, and acidosis or a lowering of the plasma carbon dioxide content does not occur. The lack of these side effects is of importance in any consideration of the ambulatory wounded and in the transportation by air of injured patients. Against these favorable factors is the known ability of the drug to produce renal damage. Observations made by my associates and me show that one can expect that in about 1.7 per cent of patients receiving average doses of this drug either microscopic or gross hematuria will develop, while in 0.4 per cent oliguria, azotemia, or anuria develops. It is known that a decreased fluid intake, with a resulting decrease in the output of urine, predisposes a patient to this type of renal complication. Hence, when water is scarce, as in desert warfare, or when temperatures are high and loss of body water is great, the threat of kidney damage might be considered a deterrent to the use of sulfadiazine. However, the

occurrence of this complication appears to be greater when sulfapyridine or sulfathiazole is administered, and one must remember that sulfanilamide produces hemolytic anemia in about two per cent of patients to whom it is given. After an evaluation of the various factors involved, it seems reasonable to conclude that, while sulfadiazine can produce serious toxic reactions, it is the least toxic of the four commonly used sulfonamide drugs, and is the drug of choice for the peroral prophylaxis of contaminated wounds and for the peroral therapy of infected wounds. If sulfadiazine is not available, sulfanilamide or sulfathiazole should be used in the order named in the peroral prophylaxis or therapy of contaminated or infected wounds.

Confusion exists in respect to the topical use of sulfonamide compounds. For example, it is commonly assumed that because sulfathiazole is more effective than sulfanilamide in the systemic therapy of staphylococcic infections, its topical use is always indicated when the possibility or the presence of staphylococcic infection exists. This assumption is not necessarily correct because various factors, such as the physical characteristics and solubility of the drug, its antibacterial effect in the upper ranges of its solubility, its rate of diffusion and absorption from the local lesion, the effect produced by its local implantation on tissue repair and wound healing, and the systemic toxic effects which the drug may produce, enter into any consideration of the selection of the drug of choice for topical use in the prevention or treatment of contaminated or infected wounds.

It has often been observed that when too finely powdered sulfonamide compounds are placed in wounds they tend to "cake." Sulfonamide compounds for topical use, consisting of large crystals or coarsely ground forms of these drugs, dissolve slowly in wounds and tend to initiate foreign body reactions. While the ideal crystal size of these compounds is not definitely known, it has been shown that satisfactory results can be obtained when crystalline sulfanilamide screened to 40 to 80 mesh is used.

The solubility and diffusibility of the compounds under consideration for local use is of importance. Sulfanilamide is soluble

in tissue fluids to the extent of from 1200 to 1500 mg. per 100 cc., and has been shown by Hawking to diffuse rapidly through living tissue and fairly well through dead tissue. This observer has demonstrated that sulfathiazole, sulfapyridine, and sulfadiazine are much less soluble (184, 61 and 124 mg. per 100 cc. in human serum at 36° C. respectively) than is sulfanilamide, and that sulfapyridine and sulfathiazole diffuse more slowly through living tissues. In our experience, sulfadiazine behaves like sulfapyridine as far as diffusion is concerned. This variation in the solubility of the drugs is important in estimating the possible antibacterial effects of these compounds when they are employed as topical agents, and it has been shown *in vitro* that in the upper range of its solubility sulfanilamide seems to be as effective an antibacterial agent as are the other sulfonamide compounds at their limits of solubility. This observation is important in the consideration of the sulfonamide drug of choice for local use in the prophylaxis and treatment of wound infections.

As has been pointed out, sulfanilamide diffuses more rapidly from the site of its implantation than do the other sulfonamides, and following the topical use of crystalline sulfanilamide in closed wounds peak concentrations of the drug in the blood can be expected in from 6 to 12 hours, with absorption and excretion of the drug being practically completed within 48 hours unless massive doses of sulfanilamide have been used locally. The peak concentrations of this drug in the blood are considerably higher than those noted following the local use of sulfathiazole, sulfapyridine, or sulfadiazine in wounds that are closed.

The latter compounds, because of their lower solubilities and rates of diffusion, are absorbed and excreted more slowly than is sulfanilamide, and in the instance of sulfadiazine we have noted that following the implantation of 5 Gm. of the drug in an extraperitoneal wound of the abdominal wall absorption of the drug continued for more than two weeks.

There is not a great deal of information available regarding the absorption of sulfonamide compounds from open wounds.

Veal and Klepser have reported that the instillation of 7.5 Gm. of sulfanilamide into an "open clean wound (pilonidal sinus excision)" produced a peak concentration of the drug of 2 mg. per 100 cc. within five hours, and at 42 hours very small amounts (less than 0.5 mg. per 100 cc.) of the drug were found in the blood. Another of their patients suffering from an open wound of the abdominal wall was given the daily implantations of 5 Gm. of sulfanilamide, followed by a gradual rise of the concentration of the drug in the blood to 12 mg. per 100 cc. on the sixth day. At the end of 36 hours the concentration of sulfanilamide in the blood was 3 mg. per 100 cc. These observations, coupled with those of our own, lead us to believe that excessive concentrations of sulfanilamide are not to be expected following its use in open wounds. In burns, the opposite seems to be true. Hooker and Lam have shown that when crystalline sulfanilamide is applied to second or third degree burns, absorption may be rapid and excessive concentrations of the drug may occur in the blood. Our own observations show that sulfathiazole and sulfadiazine are less readily absorbed from open wounds than is sulfanilamide.

The differences in the solubility of the various sulfonamide drugs appear to bear some relation to their effects on wound healing. It has been shown that in concentrations up to approximately 500 mg. per 100 cc., sulfanilamide has little if any effect on the multiplication of fibroblasts in tissue cultures and that, while this drug does inhibit certain cellular functions in higher concentrations, the recovery of the cells from its unfavorable action is rapid and complete when they are removed from excessive concentrations of the drug. Sulfathiazole has been shown to be the least favorable for growth at any assigned concentration, and, as far as sulfapyridine and sulfadiazine are concerned, their limited solubility does not permit the accurate testing of their effects on cells in tissue cultures.

It seems well established that the degree of solubility of the various sulfonamide drugs has a definite bearing on their ability to produce foreign body reactions when they are implanted locally. Sulfanilamide, because of its high solubility, is least

likely to produce this reaction within wounds, with sulfathiazole, sulfapyridine, and sulfadiazine in the order named having increasing possibilities of producing such a reaction.

As far as direct toxic effects on various types of tissue are concerned, there is disagreement concerning the action of the sulfonamide drugs. Russell and Falconer reported that the application of finely powdered sulfanilamide or sulfapyridine to the leptomeninges or the cortex of the rabbit did not produce appreciable damage within four days. Hurteau has confirmed and extended these observations, and has further reported that while sulfadiazine is slowly absorbed from brain tissue no glial reaction occurs after the implantation and but a slight foreign body reaction in the meninges. Taffel, on the other hand, has noted that all of the commonly used sulfonamides produced a mild inflammatory reaction when applied to the cortex in monkeys. Sulfathiazole seemed to produce the most intense inflammatory response, while sulfadiazine caused the most severe foreign body reaction. These observations are of especial interest in view of the recent report of Watt and Alexander. These observers noted that the application of crystalline sulfathiazole to the frontal cortex in both human beings and dogs frequently produced epileptiform convulsions. This phenomenon did not occur when sulfanilamide, sulfapyridine, or sulfadiazine was used.

Taffel and Harvey reported that the local application of crystalline sulfanilamide did not interfere with the healing of experimental wounds in the stomachs of rats. Harbison and Key have confirmed this observation and have further reported that the implantation of crystalline sulfanilamide did not disturb the healing of wounds produced in the abdominal walls of rats, nor did this drug produce adhesions when introduced into the peritoneal cavity of rats.

Glynn states that crystalline sulfanilamide has "a slight but definite toxic reaction on striped muscle," but that this drug does not inhibit fibroblastic proliferation in wounds produced in rabbits. Taylor, however, has reported that all these drugs

produced inflammation tissue reactions when implanted into wounds in dogs, and that in the case of the less soluble drugs the reactions may be so severe that actual tissue destruction and sterile abscess formation occur. Finally, Bick has recently observed that "the local application of sulfonamide drugs to wounds of the soft tissues or clean-cut operative incisions, in which primary suture is indicated, retards healing by at least 50 per cent of the time factor and promotes extensive cutaneous scarring."

As has been previously described, the local application of the sulfonamide drugs to wounds may cause an exudation of tissue fluids, which in the instance of a tightly sutured wound may cause tension and delay wound healing. Our observations lead us to believe that sulfathiazole and sulfadiazine are more likely to produce such an exudation of fluid than is sulfanilamide.

Out of the welter of conflicting experimental and clinical reports just reviewed one fact seems to emerge, namely, that while the local implantation of sulfanilamide may interfere to a certain degree with wound healing, it appears to be the least harmful of the commonly used sulfonamides to regenerating tissues.

Thus, when all the factors have been considered, it seems reasonable to choose sulfanilamide as the drug of choice for the prophylaxis and treatment of contaminated and infected wounds.

In considering the peroral prophylactic dose of sulfadiazine needed for the prevention of wound infections, civilian injuries must be differentiated in general from war casualties. In the first instance, definitive surgical treatment will probably be given promptly, and in most cases the administration of sulfadiazine by mouth can be deferred until just prior to or after definitive surgical treatment. In the case of persons wounded as the result of enemy action, definitive surgical treatment may be delayed for many hours; therefore, the prophylactic dose of sulfadiazine should be given as soon as possible after the wound has been incurred.

For adult civilian injuries, the initial peroral dose of sulfadiazine should be 2 to 4 Gm., given either immediately before or after definitive surgical treatment, this to be followed by 1 Gm. of the drug every six hours for two days, following which doses of 0.5 Gm. every six hours should be administered for eight days.

For adults wounded as the result of enemy action, the initial peroral dose of sulfadiazine should be 4 Gm. This should be given as soon as possible. After this initial dose no more of the drug should be given by mouth until after definitive surgical treatment has been completed. Then sulfadiazine 1 Gm. every six hours should be administered day and night for from seven to ten days. If infection occurs despite the attempt at prophylaxis, the administration of the drug should be continued until the infection is under control. It is important to maintain a daily output of urine of at least 1000 cc. during the period of treatment in order to lessen the possibility of the occurrence of renal complications. If sulfadiazine is not available, sulfanilamide or sulfathiazole prescribed in the same dosage may be used. For injured children doses of these drugs should be adjusted according to the weight of the child in comparison with the adult dose.

There is a tendency at the present time to dump sulfonamide compounds haphazardly into wounds. This is a bad practice, and it should be emphasized that the implantation of sulfanilamide should be done carefully in order that all parts of the surface of the exposed wound will be in contact with the drug. A shaker-top container makes this easy, although many physicians prefer to use a powder atomizer for applying sulfanilamide locally.

In wounds that are closed by primary suturing, the amount of crystalline sulfanilamide implanted should approximate 0.05 Gm. per square inch of wound surface. This represents a light "frosting" of the wound. In contaminated wounds in which closure is not indicated, or in infected wounds, 0.1 Gm. of crystalline sulfanilamide per square inch (6.25 sq. cm.) of wound surface should be used. This represents a heavy "frosting" of the

wound. On the basis of our present experience it would seem that not more than 10 Gm. of sulfanilamide should be given locally to any given patient within a 24-hour period.

The combination of sulfadiazine by mouth and sulfanilamide locally will produce sulfonamide concentration in the blood of from 6 to 16 mg. per 100 cc. in the first 24 hours in patients whose wounds are closed. If, however, the wounds are left open, concentrations of the sulfonamide in the blood of from 5 to 10 mg. per 100 cc. will generally be noted in the first 24 hours of therapy.

It has been mentioned previously that peroral therapy with sulfadiazine may be discontinued in from seven to ten days if symptoms and signs of infection are lacking. However, experience has repeatedly shown that it is necessary to repeat the local application of sulfanilamide to wounds at each dressing period if both primary and secondary wound infection is to be prevented. Local therapy with sulfanilamide should be continued until healing is complete.

As has been pointed out before, the successful treatment of contaminated or infected wounds is influenced by the amount of necrotic tissue or purulent material in the wounds, because these substances act as sulfonamide inhibitors. Therefore, if a wound shows evidence of infection, it should be gently irrigated with isotonic solution of sodium chloride at each dressing or, perhaps better, with a mild oxidizing agent such as a 1:3300 solution of azochloramid. (Such solutions should be stored away from the light in brown glass bottles.) It has been shown that the latter compound is effective in neutralizing the effects of sulfonamide inhibitors, and indeed there is some evidence that azochloramid acts synergistically with the sulfonamides. Recent experience has also shown the value of utilizing dressings moistened with a 1:3300 solution of azochloramid in the prophylaxis of contaminated and the treatment of infected wounds. These dressings can be placed in the wound after crystalline sulfanilamide has been applied and sealed over with boric acid ointment or petrolatum gauze to prevent them from drying. It

is important to keep the wound dressing moist in order to prevent the caking of implanted sulfonamides.

However, while sulfonamides have proved a great boon in the prophylaxis and treatment of infected wounds, Bick² points out that the local application of these drugs to wounds of the soft tissues or clean-cut operative incisions in which primary suture is indicated retards healing by at least 50 per cent of the time factor and promotes excessive cutaneous scarring. In extremity surgery this delay in healing time may postpone necessary active motion and massage; in plastic skin repair it may interfere with a cosmetic result. Therefore, unless infection is anticipated because of the circumstances of the lesion or of the operation, the use of topical sulfonamide therapy may be an unnecessary burden. On the other hand, the author believes that its use in cases in which infection may be anticipated, such as in wounds contaminated under field conditions, is now almost obligatory.

Overton³ in a report on 356 open wounds, in 285 of which one of the sulfonamides was implanted locally, concedes the value of the sulfonamides in badly disrupted wounds which cannot be thoroughly cleansed and débrided, but says their use cannot supplant good surgery. His conclusions follow:

1. The local use of the sulfonamides has not improved the results in the treatment of open wounds when used as an adjunct to good surgery during the contaminated stage; however, it was found not to delay the healing time.

2. All of the sulfonamides produced some local tissue irritation as evidenced by the increase in serum and tendon adhesions.

3. The results of this study indicate the local use of the sulfonamides is not necessary in the early treatment of open wounds which can be thoroughly cleansed and débrided. These drugs may produce enough irritation to contraindicate their use in such cases.

4. The use of the sulfonamides may be of definite value when administered in badly disrupted wounds which cannot be thoroughly cleansed and débrided. When combined with the

use of one of the drugs by mouth, sulfonamides are invaluable in this type of case.

5. The criteria of good early treatment of any open wound is thorough cleansing and the removal of all contaminated and nonviable material followed by wound support and rest. Under no circumstances should the sulfonamides be substituted for this treatment.

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Appendix

SOMETIME after the present world conflict there will be made available for civilian use a new drug which possibly will supplant the sulfa drugs in many pathologic conditions. This drug is penicillin, a derivative from a mold.

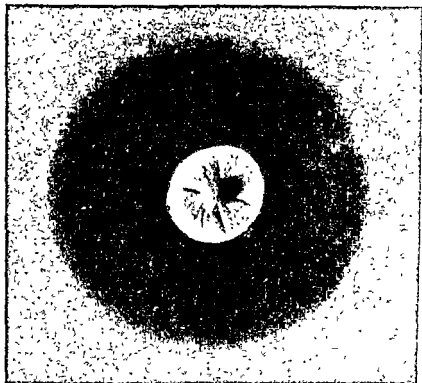
Penicillin was first discovered in 1929 by Dr. Alexander Fleming, working in the University of London. He noticed that a petrie dish growing a profusion of bacteria contained a speck of mold surrounded by a clear area free from organisms. Quite evidently there was something being excreted by this mold that killed the surrounding organisms. The mold was identified as *Penicillium notatum* and after much research its active principle effective against bacteria was isolated. Not much more was done with penicillin until its possibilities in war wounds caused intense research to begin again, this time on both sides of the Atlantic. The manner of its action against bacteria is still not clearly understood, but it is presumed that like the sulfa drugs it prevents division and increase of the microorganisms and that then the natural body defenses have an opportunity to overcome the infection.

Unfortunately, to date no one has succeeded in synthesizing penicillin and it has not so far been possible to produce it on a large scale. All that is produced now goes to the armed forces.

The new drug is said to be especially effective against staphylococcal infections where the sulfonamides are least effective. Staphylococcal septicemia, osteomyelitis, war wounds, gonococcal infections, and a few cases of pneumonia are some of the infections which have responded to penicillin. Streptococcal endocarditis and arthritis are not affected by it. No toxic reactions have been reported to date.

There is no question from the reports available that penicillin holds great promise for the future, but there has been too little

experience with it yet to evaluate its place in therapeutics. No doubt, when extensive clinical experience fixes its place and shows us its limitations, we will find that it is indicated in certain conditions while the sulfa drugs are indicated in others.



(Courtesy E. R. Squibb & Sons, N. Y.)

Fig. 1—The therapeutic possibilities of *Penicillium notatum* were first realized when it was found that a colony of this mold growing in a culture of staphylococci was surrounded by a clear zone in which bacterial growth was prevented.

However, it may be years before penicillin is available in sufficient quantity to help the average physician, and until that time arrives he has at hand the sulfonamides with all their potency in indicated conditions.

The following data on the use of penicillin are from the report of the Committee on Chemotherapeutic and Other Agents, Di-

vision of Medical Sciences, which appeared in the Journal of the A. M. A. 122:1218 (Aug. 28) 1943:

Mode of Administration: Solutions of penicillin were given intravenously, intramuscularly, and topically, including local injection into the pleura, pericardium, and joints and into the subarachnoid space. In giving penicillin intravenously, constant infusions were used in many cases, whereas repeated injections at two-, three-, or four-hour intervals were employed in others. When it became necessary to continue treatment over a period of several weeks, it was necessary in many cases to use various routes of administration, including constant intravenous infusion and repeated intravenous or intramuscular injections. Some patients tolerated intramuscular injections better than repeated intravenous injections; others did not.

In the treatment of meningitis, empyema, and surface burns of limited extent, penicillin was used topically; that is, injected directly into the subarachnoid space or the pleural cavity or applied locally.

Concentration and Volume of Penicillin: For intravenous use, concentrations of 1000 Oxford units per cubic centimeter or less were used at each injection. When a constant intravenous infusion was used the concentration was varied, depending on the total dosage during a 24-hour period. The rate of injection in some cases varied from 5000 to 10,000 units an hour day and night; that is, 120,000 to 240,000 units every 24 hours. In others smaller amounts of solution were injected. This was regulated so that the rate of delivery was between 75 and 100 cc. an hour. The penicillin was dissolved in saline solution or five per cent dextrose solution and allowed to run into the veins slowly or injected directly into the rubber tubing at periodic intervals.

With intramuscular injections it is important to keep the volume as low as possible in order to avoid local discomfort at the site of injection. The usual practice has been to employ a concentration of 5000 units per cubic centimeter. In general, there was no local reaction, but there may be some local soreness at the site of injection in some patients.



(Courtesy E. R. Squibb & Sons, N. Y.)

Fig. 2—While stored in the culture room the surface of the medium gradually becomes covered with a corrugated, green-blue-gray growth with velvety texture. As it grows the mold produces the powerful antibacterial agent, penicillin, which diffuses into the liquid beneath.

Dosage: The total amount of penicillin administered in Oxford units has varied tremendously from one case to another. There were also many variations in the total amount given with each injection, the interval of time between injections, and the total duration of the treatment. These are natural variables in the investigation of any new drug, especially when information is being accumulated with only a limited supply of valuable material in several different infections. At the beginning of our studies it was common practice to give 5000 units intravenously every four hours day and night; that is, 30,000 Oxford units every 24 hours. This amount was found to be adequate in some infections but was totally inadequate in others. Indeed, the dosage schedule varied from 1000 to 25,000 units per hour, depending on the kind and severity of infection. In view of the variation in the dosage schedule, it will be well to outline the practice at the present time. Before presenting the details it should be said that the question of adequate or optimum dosage has not been clearly defined. The objective in treatment should be the maintenance of a sufficient concentration of penicillin in the blood to inhibit completely the growth of the individual infecting organism.

Various methods have been used to titrate penicillin in the blood serum and body fluids and exudates (Fleming,¹ Abraham *et al.*² and Rammelkamp³). They all have as their objective the determination of the amount of penicillin that will inhibit the growth of a constant number of a standard strain of hemolytic streptococcus or Staph. aureus or of the patient's own strain of infecting organism. When facilities are available, such methods should be employed in the treatment of individual cases in order to determine whether sufficient amounts of penicillin are being administered.

Other methods of assessing adequate dosage are the signs of clinical response. These must be followed with great care and should include not only the response of the temperature and pulse rate, but also the change in constitutional symptoms, the results of blood culture, and the effect on the local infection.

Absorption, Excretion, and Distribution: The absorption, excretion, and distribution of penicillin has been studied by Rammelkamp and Keefer,⁴ and the literature on the subject has also been reviewed by them. Blood concentrations of penicillin and urinary excretion of penicillin were determined after the administration of 5000 to 40,000 Oxford units by various routes. Their summary was as follows:

Intravenous injection of penicillin resulted in high initial concentration in the blood plasma, which was followed by an abrupt fall. Traces of penicillin were found in the blood for 30 to 210 minutes after the injection, the length of time depending on the amount administered. The sharp fall noted in the serum concentration immediately after the injection was associated with an increased excretion in the urine. The average excretion after intravenous injection was 58 per cent of the administered dose.

Penicillin was rapidly absorbed when given intramuscularly and slowly absorbed after subcutaneous injections. Excretion in the urine was rapid following intramuscular injections and delayed after subcutaneous injections.

Absorption from the body cavities was delayed, and this was reflected in the slow excretion of penicillin by the kidneys. The total amount found in the urine was somewhat lower than that obtained following intravenous injection. Fluid aspirated from the pleural and joint cavities 22 and 15 hours after the injection showed appreciable amounts of penicillin remaining.

Administration of penicillin by enteral routes showed that absorption from the duodenum was rapid, whereas oral and rectal doses were poorly absorbed. These findings may be explained by the inactivating effect on penicillin of acid and *Escherichia coli*. After oral, intraduodenal and rectal administration, the average amount excreted in the urine was extremely small.

In the presence of renal failure penicillin was not excreted rapidly, and as a result high concentrations were maintained in the blood stream after intravenous injections.

Studies on the distribution of penicillin showed that the substance failed to penetrate the red cells in significant amounts. In general the average concentration found in erythrocytes was less than 10 per cent of the plasma concentration. No penicillin was found in the spinal fluid, saliva, or tears in subjects receiving it intravenously.

Rammelkamp and Helm⁵ have shown that human saliva, bile, and succus entericus do not inactivate penicillin, but gastric

juice destroys it rapidly at body temperature. The destructive action appears to be due to hydrochloric acid and not to pepsin. In two patients with pernicious anemia and achylia gastrica the absorption of penicillin, when administered by mouth, was greater than that of normal subjects.

Aside from the excretion of penicillin in the urine, there is good evidence that it is excreted by the liver, since it can be found in the bile in higher concentration than in the blood stream. None has been demonstrated in the gastric juice.

Intrathecal Injection: With regard to the intrathecal injection of penicillin, in normal subjects the substance is slowly absorbed and slowly excreted in the urine following the injection of 5000 or 10,000 Oxford units.⁶ It may be detected in the spinal fluid for at least 31.5 hours after the injection of 10,000 Oxford units. There is some evidence that penicillin is slightly irritating to the normal meninges, and the injection of 10,000 Oxford units into the subarachnoid space may be followed by headache, vomiting, increased intrathecal pressure, and pleocytosis in the spinal fluid. Smaller amounts cause less intense symptoms.

In patients with meningitis, absorption of penicillin from the intrathecal space is more rapid than in normal subjects, and a greater amount of that injection is excreted in the urine. Penicillin can be detected in the spinal fluid 24 hours after its injection.

We have been unable to detect penicillin in the cerebrospinal fluid after intravenous or intramuscular injection; for this reason it is well, for the time being at least, to use penicillin both intravenously and intrathecally in the treatment of meningitis.

Penicillin-resistant Strains: It has been demonstrated by Rammelkamp and Maxon⁷ that various freshly isolated strains of *Staph. aureus* vary only slightly in their susceptibility to the antibacterial action of penicillin. When, however, a given strain of *Staph. aureus* was grown in increasing concentrations of penicillin over a long period of time, it was possible to make

the organism resistant. These investigators were also able to demonstrate that an increase in the resistance of *Staph. aureus* may also occur during the course of penicillin therapy for localized infections in man.

It has been shown⁸ that strains of pneumococci, staphylococci, and hemolytic streptococci may be made resistant to penicillin by exposing them to it continuously for a long period of time both *in vitro* and *in vivo*. It is of considerable interest that penicillin-fast strains of pneumococci are susceptible to the sulfonamides and that sulfonamide-resistant strains of pneumococci are susceptible to penicillin. Moreover, McKee and Houck⁹ have shown that an increase in the resistance of organisms to penicillin is associated with a proportional loss of virulence, an observation that is in striking contrast to the retention of virulence by sulfonamide-resistant cultures.

Obviously, more information is needed concerning penicillin-resistant strains and their mode of production, since it may aid one in interpreting the clinical results or failure. It should be reemphasized that, once a strain increases in resistance it loses its virulence and seems to be changed permanently as far as penicillin is concerned, but it remains susceptible to the sulfonamides. Also resistance is produced only after continuous exposure to the action of penicillin.

Method of Preparing Penicillin for Treatment: Penicillin is supplied in ampules of 5000 units, 10,000 units, 25,000 units, 100,000 units, and 1,000,000 units. As penicillin is extremely soluble, it may be dissolved in small amounts of sterile, distilled, pyrogen-free water, in sterile isotonic solution of sodium chloride, or in five per cent dextrose solution. When large unit sizes are being used in hospitals, the contents of the ampule should be dissolved in water or saline solution so that the final concentration is 5000 units per cubic centimeter. This solution should be stored under aseptic precautions in an ice box and made up freshly every day. Solutions for local or parenteral use may be diluted further, depending on the concentration desired.

A. For intravenous injection:

1. The dry powder may be dissolved in sterile isotonic solution of sodium chloride in concentrations of 1000 to 5000 units per cubic centimeter for direct injection through a syringe.
2. The dry powder may be dissolved in sterile saline solution or five per cent dextrose solution in lower dilution (25 to 50 units per cubic centimeter) for constant intravenous therapy.

B. For intramuscular injection:

1. The total volume of injections should be small; that is, 5000 units per cubic centimeter of isotonic solution of sodium chloride.

C. For topical application:

1. The powdered form of the sodium salt is irritating to wound surfaces and should not be used.
2. Solutions in isotonic solution of sodium chloride with a concentration of 250 units per cubic centimeter are satisfactory. For resistant or more intense infections this concentration may be increased to 500 units.

Toxicity and Reactions

One of the remarkable features of penicillin is its relatively low toxicity and the extremely low incidence of a systemic nature. This is all the more remarkable in view of the fact that the material that is available for clinical testing at present is perhaps not more than 10 to 15 per cent pure penicillin.

Chills and Fever: These were recorded in 12 cases and fever in 5. In several it was difficult to attribute these reactions to the penicillin, since chills and irregular fever were present before treatment was started and they continued for a short period following treatment. In others, however, it was plain that these reactions were definitely related to the injection of penicillin. This statement is supported by the observation that the injection of 10,000 units of penicillin from some lots caused chills and fever, whereas the injection of 5000 units from the same lot caused no reaction. These reactions were transitory, and aside from the temporary discomfort to the patient they caused no difficulty. In a few patients, who were afebrile before treatment was begun, low-grade fever varying from 100° to 101° F. would

TABLE 1—DETAILED SUMMARY OF 500 CASES

<i>Diagnosis</i>	<i>No. of Cases</i>	<i>Recovery or Improvement</i>	<i>Death</i>	<i>No. Effect</i>
Staphylococcus aureus infection:				
With bacteremia:				
Sepsis without obvious port of entry.	10	9	.	1
Acute osteomyelitis.	22	18	2	2
Pyelonephritis	5	2	3	
Infections of skin and subcutaneous tissues, including carbuncles, furuncles and cellulitis	10	10	.	
Thrombophlebitis with or without pulmonary embolism	3	2	1	
Burns	5	2	3	
Pneumonia	5	3	2	
Arthritis	1	1		
Subarachnoid abscess	1	1	.	
Meningitis	2	1	1	
Cavernous sinus thrombosis	2	1	1	
Postoperative wound infection	3	1	2	
Epidural abscess	2	2		
Orbital cellulitis	1	1		
Endocarditis	9		9	
Pansinusitis.	1		1	
Dissecting aneurysm of aorta	1		1	
Cancer of rectum	1		1	
Uremia from sulfadiazine	1		1	
Aplastic anemia.	2		2	
Multiple abscesses	4		4	
Totals. . .	91	54	34	3
Without bacteremia				
Osteomyelitis.	55	48		7
Empyema. . .	9	7	1	1
Postpartum sepsis	2	2	.	
Infections of the skin and subcutaneous tissues . . .	23	19		4
Laryngotracheitis	1	1	.	
Brain abscess. .	3	1	2	
Burns. . .	9	5	4	
Mastitis. .	5	5	.	
Pneumonia. .	3	3		
Lung abscess. . .	3	2	1	
Wound infection.	1	1		
Parotitis. . . .	1	1		
Epidural abscess. . . .	1	1		

TABLE 1—Continued

<i>Diagnosis</i>	<i>No of Cases</i>	<i>Recovery or Improvement</i>	<i>Death</i>	<i>No Effect</i>
<i>Without bacteremia (Continued)</i>				
Postoperative infection .	4	3	.	1
Abscess, 1 case each (neck, abdominal wall, throat, right lower quadrant of abdomen, retroperitoneum mouth, submentum, cheek, scalp) . .	9	6	.	3
Arthritis .	1	1	.	
Recticulum cell carcinoma.	1		1	..
Meningitis .	3	1	2	
Prostatitis	2	2		
Totals .	137	109	11	16
<i>Streptococcic infections other than bacterial endocarditis:</i>				
<i>Hemolytic streptococcus (23 cases):</i>				
Postabortum sepsis .	1	1		
Bacteremia with meningitis	1	1		
Conjunctivitis	1	1		
Osteomyelitis of spine.	2	2		
Mastoiditis with bacteremia	1	1		
Ulcer of skin	3	2		1
Microaerophilic ulcers of skin.	1			1
Multiple abscesses of skin.	1	1		
Skin infection and subphrenic abscess.	1		1	
Empyema . . .	2	2		
Mastoiditis and pericarditis.	1	1		
Abscess of axilla.	1	1		
Post-tonsillitis sepsis.	2		2	
Cirrhosis of liver. .	1		1	
Meningitis	2		2	
Chronic nephritis.	1		1	
Carrier. . . .	1			1
<i>Nonhemolytic streptococcus (4 cases):</i>				
Pyelonephritis with endocarditis	1			1
Brain abscess	2		2	..
Multiple abscesses . .	1		1	
<i>Anaerobic streptococcus (6 cases):</i>				
Septic abortion	5	3	2	
Skull fracture, meningitis	1	1		
Totals	33	17	12	4

TABLE 1—Continued

<i>Diagnosis</i>	<i>No. of Cases</i>	<i>Recovery or Improvement</i>	<i>Death</i>	<i>No Effect</i>
Pneumococcic infections				
Pneumonia	42	35	6	1
Meningitis	21	7	14	
Meningitis with endocarditis	2		2	
Endocarditis	6	1	5	
Pericarditis	1		1	
Pneumonia with empyema	2		1	1
Empyema	2	2		
Totals	76	45	29	2
Gonococcic infections	129	129*		
Meningococcic infections	5	4	1	
Subacute bacterial endocarditis	17	3	4	10
Miscellaneous infections:				
Atypical pneumonia	1			1
Moniliasis	1			1
Agranulocytosis	1	1		
Micrococcus tetragenus sepsis	1	1		
Ulcerative colitis	1	1		
Actinomycosis	3	1	2	
Micrococcus auranticus sepsis	1			1
Escherichia coli—nonhemolytic streptococcus abscesses	1			1
Subscapular abscess—mixed infection	1	1		
Putrid abscess	1		1	
Totals	12	5	3	4

* Four of these cases showed only temporary improvement.

occasionally occur and last for several days. This was noticeable particularly in those patients who were receiving penicillin in large amounts continuously.

Urticaria: Urticarial eruptions were reported in 14 cases. Their cause remains obscure, since in some of the cases the urticaria did not appear for several days after penicillin was discontinued, in others it did not recur when penicillin was

again injected, and in still others it developed during the exhibition of it. Whether these reactions are due to some impurity in the penicillin cannot be stated at present. In several cases in which penicillin has been given after an attack of urticaria there have been no signs of recurrence. The urticaria usually disappears temporarily following the injection of epinephrine.

Thrombophlebitis: This complication at the site of injection was recorded in 19 cases. It has been noted with certain lots of material and is likely to occur when injections are made repeatedly and when concentrated solutions are used. There is also some individual susceptibility to thrombophlebitis, since in several of the reported cases penicillin from the same lot injected into one patient would be followed by thrombophlebitis, whereas it would cause no reaction in a second patient. Pain along the course of the vein during the injection of material has been complained of by some patients.

Miscellaneous Complaints: Transitory attacks of throbbing pain in the head, flushing of the face, tingling in the testes, pains in the muscles, and constriction in the chest have been observed. All these complaints last only a few minutes and disappear spontaneously. It has been found that some impurity carried over from the extraction process used to remove pyrogens was responsible for these reactions. Passing the solutions through a Seitz filter removed the substances, and recent lots of penicillin have not caused these reactions.

Aside from the patients who developed urticaria, there has been none who has developed any signs of sensitivity to penicillin. Many patients have received several prolonged courses of penicillin at varying intervals of time, and in none of them so far have any reactions been observed to a second or even a third course of treatment.

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